EuPA Open Proteomics 10 (2016) 50–55

Contents lists available at ScienceDirect

EuPA Open Proteomics

journal homepage: www.elsevier.com/locate/euprot

Developmental origins of metabolic disorders: The need for biomarker candidates and therapeutic targets from adequate preclinical models

Antonio Gonzalez-Bulnes[a,b,*], Susana Astiz[a], Marta Vazquez-Gomez[c], Consolación Garcia-Contreras[d]

[a] Comparative Physiology Lab-RA, SGIT-INIA, Madrid, Spain
[b] Department of Veterinary Medicine, University of Sassari, Sassari, Italy
[c] Faculty of Veterinary, UCM, Madrid, Spain
[d] Department of Animal Genetics, SGIT-INIA, Madrid, Spain

ARTICLE INFO

Article history:
Received 10 November 2015
Received in revised form 20 December 2015
Accepted 5 January 2016
Available online 7 January 2016

Keywords:
Animal-models
Biomarkers
Developmental-programming
Metabolic-syndrome
Obesity

ABSTRACT

The investigation on obesity and associated disorders have changed from an scenario in which genome drove the phenotype to a dynamic setup in which prenatal and early-postnatal conditions are determinant. However, research in human beings is difficult due to confounding factors (lifestyle and socioeconomic heterogeneity) plus ethical issues. Hence, there is currently an intensive effort for developing adequate preclinical models, aiming for an adequate combination of basic studies in rodent models and specific preclinical studies in large animals. The results of these research strategies may increase the identification and development of contrasted biomarkers and therapeutic targets.

1. Introduction

Currently, nutrition-related disorders (obesity, metabolic syndrome and diabetes) are in the focus of intense research and debate. First, the appearance of obesity and associated conditions like diabetes is linked to other non-communicable disorders; e.g. cardiovascular disease. In fact, 50% of deaths caused by diabetes are related to cardiovascular disease (primarily heart disease and stroke; [1]). Second, obesity and associated disorders were traditionally reported in adult individuals of wealthy populations from high-income countries. However, in recent years, the global changes in lifestyle and dietary patterns have modified the distribution of the diseases and therefore obesity and diabetes affect both children and adults of different socioeconomic classes in both developed and developing countries [2]. Hence, obesity was declared a global pandemic by the World Health Organization (WHO) in 2005, when the affected population reached 400 million of adults and at least 2.6 million of people were dying each year as a result of being overweight or obese. Furthermore, WHO predicted that around 2.3 billion adults would be overweight and 700 million would be obese by 2015 (http://www.who.int/features/factfiles/obesity/en/index.html). This prediction was not too much inaccurate since in the last year, 2014, around 1.9 billion of adults were reported to be overweight and 600 million to be obese (http://www.who.int/mediacentre/factsheets/fs311/en/). These data mean that 39% of adults are overweight and 13% are obese; of them, 9% are affected by diabetes. Diabetes caused 1.5 million deaths in 2012; more than 80% of them occurring in low- and middle-income countries (http://www.who.int/mediacentre/factsheets/fs312/en/).

Moreover, the problem is aggravated by the causal relationship among nutrition-related diseases and other non-communicable diseases (i.e. renal, immune, inflammatory and reproductive disorders, and cancer [3–7]). Hence, the epidemics is becoming a major worldwide public health problem since it does not only affects directly life-quality and wellbeing of individuals but also constitutes a strong economic challenge to health-care systems and governmental administrations. Thus, there is an urgent need to tackle the situation, by both increasing research in the area and developing adequate strategies for prevention and treatment.

The studies performed in the last decades have changed substantially the vision of the causal factors of obesity and associated disorders. We have moved from a gene-centric static perspective, in which genome drove the phenotype with secondary

* Corresponding author at: Comparative Physiology Lab, RA-INIA, Avda. Puerta de Hierro s/n., 28040 Madrid, Spain.
E-mail addresses: bulnes@inia.es, agbulnes@gmail.com (A. Gonzalez-Bulnes).

http://dx.doi.org/10.1016/j.euprot.2016.01.001

influence of lifestyle and nutrition, to a much more holistic and dynamic approach in which environmental, parental, prenatal and early-postnatal conditions are strongly determinants of postnatal development and homeostasis and therefore health status and disease risks. In this scenario, the development of proteomics and other "-omics" during the last years is giving a complimentary tool that may help to accurately elucidate the condition and identify therapeutic targets [8–13].

2. The Developmental Origins of Health and Disease (DOHaD)

The DOHaD concept points out that prenatal and early-postnatal conditions (mainly nutrition and lifestyle) determine growth, life-time fitness/obesity and the risks for non-communicable diseases via epigenetic changes induced during development (reviewed in Ref. [14]). In all the mammalian species, foetal development is dependent on adequate transfer of oxygen and nutrients from the mother to the foetus via the placenta. Inadequate maternal conditions (e.g. deficiency or excess in food intake or hypoxia) and/or metabolic disturbances (e.g. obesity, metabolic syndrome or diabetes) and insufficient placental function may affect the supply of oxygen and nutrients to the foetuses. Hence, such conditions may affect foetal development and may compromise homeostasis, metabolism and health of the offspring throughout life, and even may affect subsequent generations (transgenerational programming [15]).

In case of maternal food-intake excess, obesity and metabolic disorders, the excess in the supply of nutrients induces an excessive development of the foetuses. At birth, in situations of maternal overnutrition, neonates are frequently large-for-gestational age (LGA) and obese, having high amounts of body fat; moreover, they can manifest macrosomia with severe enlargement of heart, liver and spleen [16].

In case of maternal food intake deficiencies or hypoxia and in case of placental insufficiency, the shortage in the supply of oxygen and nutrients to the foetuses causes deficiencies in their development. The neonates are small-for-gestational-age (SGA), with reduced body-weight at birth as a consequence of a process known as intrauterine growth restriction (IUGR). In humans, the incidence of IUGR infants ranges between 7 and 15% depending on sociodemographic issues [17]. Classically, IUGR has been associated with maternal malnutrition but, currently, 60% of IUGR offspring are identified as mainly caused by placental insufficiency [18,19].

Maternal obesity and metabolic disorders may also cause IUGR [20–22], mainly due to vascular alterations affecting the placental development and function and causing foetal hypoxia [23]. Women with alterations in glucose and lipid metabolism may also develop hypertensive disorders in pregnancy (HDP). HPD includes a spectrum of disorders varying, according to severity, from chronic pre-existing hypertension and gestational hypertension to preeclampsia and eclampsia. Occurrence of HDP usually induces IUGR and SGA [24].

SGA offspring, depending on the severity of IUGR, may be predisposed to high neonatal morbidity and mortality rates, with early death or life-long alterations in their development, health and welfare [25]. In offspring with extreme IUGR, deficiencies of development are unavoidable and viability of the neonate is strongly compromised, causing death. In less-critical IUGR, the central nervous system functionality is assured but the functionality of the other organs can be severely affected. Hence, health and welfare of these IUGR offspring is compromised by gastrointestinal (alterations in development and function of the intestine, which predispose to feeding intolerance and digestive disorders), metabolic (inadequate liver development, which is essential for the metabolism of glucose, amino-acids, proteins, lipids and vitamins), respiratory (abnormalities in the airways and lungs, causing impaired respiratory function), renal (compromising homeostasis and causing hypertension) and immune disfunctions (immune depression and high susceptibility to infection) [26–30].

At adulthood, both LGA and SGA phenotypes are affected by different health complications, such as obesity, metabolic, and cardiovascular pathologies [25,31–34].

The profound implications of these disorders in perinatal survival and lifelong performance and health have boosted research efforts. The perspective on future research is based on three pillars: the complete understanding of the underlying biology of the disease, the availability of contrasted biomarkers for diagnosis, and the assessment of preventive and curative treatments. These three keystones would allow the improvement of both individualised healthcare and wide population strategies focussed on diagnostic and treatment.

3. The usefulness of animal models for the screening of adequate biomarker candidates and therapeutic targets

Biomarkers are essential tools for delineating adequacy or inadequacy of biological processes (for allowing early and accurate diagnosis) and the spectrum of biological effects of intervention strategies (for developing optimal dosage and treatment strategies). However, the a priori discovery of biomarker candidates in patient populations is difficult due to the inherent high variability of data caused by a plethora of confounding factors (including genetic, lifestyle and socioeconomic heterogeneity, as well as co-morbidities and their treatments, to name but a few). In addition, research in human beings is obviously limited by ethical issues.

Hence, preclinical studies in animal models are an important source of biomarker candidates for the systematic analysis of pregnancy disturbances and for the efficacy and safety evaluations of new treatments. The translation from basic research into practice is a long, often inefficient and costly process. The choice of appropriate animal models with adequate features is critical for the success of translational research.

Models in experimental studies on obesity and metabolic disorders have been traditionally based on laboratory rodents, especially rats and mice [35–38]. The rodents need little space, are relatively inexpensive to maintain, easy to manage, have a short life cycle, have a sequenced genome and are easily modified by genetic engineering. However, rodents are the election model for studies on a concrete mechanism but there are also certain severe limitations. The main constraints are the marked differences with humans in cell and tissue biology, metabolic and endocrine routes, and developmental patterns and physiology of organs and systems [39,40]. Moreover, placentation of rodents is a very specific evolutive strategy of these species and show large differences when compared to humans [41]. Hence, findings in rodents are very different from those in human patients in many diseases and developmental areas. Different large animal species overcome these limitations and offer numerous profitable characteristics for the discovery and testing of biomarkers.

In brief, housing and management of large animals are well-developed, behavioural patterns are diurnal and body size allows application of imaging techniques and serial sampling of large amounts of blood and tissues. Moreover, pathways regulating appetite, energy balance and adipogenesis in large animals are more similar to humans than in rodents. Finally, in the last years, the genomic analysis is well-advanced and it is possible to obtain targeted gene mutations for specific models.

The most prominent large animal model for translational studies in nutritional and metabolic disorders is the pig [42,43]. At the same time, the mammalian species with the highest rate of IUGR is the swine with an average incidence of 15–20% [44,45].

Modern swine production is mainly based on large farms (in Europe, USA, Brazil, China and other countries in South-East Asia) generating "value-for-money" products with optimised productivity and efficiency. Genetic, nutritional and reproductive strategies are main tools in modern pig production. A main approach to improve profitability consists of increasing the number of piglets born per litter (prolificacy). Nevertheless, a higher litter size limits the available uterine space for placental development and, hence, compromises placental function and causes IUGR in some of the littermates. In fact, highly-prolific sows are characterised by a high number of piglets in the litter but also by a high incidence of SGA piglets, also known as low-birth-weight (LBW) piglets [45,46]. Incidence of IUGR and LBW piglets may be also increased by maternal nutritional deficiencies [47].

Piglets affected by IUGR have a similar health status to IUGR infants (mainly characterised by gastrointestinal and metabolic disfunctions) and are therefore largely used for translational studies. Proteomics and other "-omic" techniques have been used in the last years to empower classical studies and get a more holistic picture of critical points like foetal homeostasis [48], and liver [49,50] and intestinal function [49,51,52] in neonates.

Moreover studies on incidence and pre- and postnatal consequences of IUGR and developmental programming are of highly translational value for biomedical research, but are also crucial in animal production; results will optimise animal health and welfare, as well as profitability and sustainability of the productive systems [53].

4. Processes and biomarkers of maternal and foetal metabolism

Glucose, free fatty acids (FFAs), lipids and amino acids are essential for adequate foetal development. The foetus obtains them mostly from maternal supply. Early pregnancy is characterised by hyperphagia and increased lipogenesis, which causes fat accumulation, whilst late pregnancy is characterised by reduced intake but accelerated breakdown of the previously accumulated fat depots (lipolysis; [16]). Maternal lipolysis during the last trimester of pregnancy is important for foetal development, as it produces FFA and glycerol, which, in the maternal liver, are converted into triglycerides, ketone bodies and glucose that are transferred to the foetus [54]. Hence, common biomarkers of pregnancy and foetal development are maternal fasting blood glucose, triglycerides, total cholesterol, VLDL-cholesterol, LDL-cholesterol, HDL-cholesterol, and pregnancy associated protein-A (PAPP-A) [55]. Other biomarkers may be focused on placental transporters mediating the transfer of amino acids, glucose (GLUTs), and fatty acids (FATPs) [56].

A good example is the foetal uptake of amino acids, which needs to be performed through two active transporter processes. The first, known as system A transporter (SNAT1, SNAT2 and SNAT4), facilitates the uptake of small non-essential neutral amino acids (e.g. alanine, glycine and serine) against their concentration gradient by simultaneously transporting sodium into the cell [57,58]. The second, known as system L transporter (LAT1 and LAT2), facilitates exchange of non-essential amino acids for essential amino acids (e.g. leucine and phenylalanine) against their concentration gradient, independently of sodium [59].

Glucose crosses the placenta via facilitated transport, mainly by GLU1 [60], and is generally considered to be the main energy source for developing foetuses [61]. A certain degree of maternal insulin resistance is a physiological state during pregnancy in order to facilitate the supply of glucose to the feto-placental unit, which is necessary for adequate foetal development. However, in case of women affected by severe insulin resistance and hyperglycaemia (either by pre-existing diabetes or pre-diabetes or by gestational diabetes mellitus; GDM), the foetuses are exposed to high intrauterine concentrations of glucose; their development, as a consequence, is accelerated and the result is macrosomia. Diabetes also alters the expression and activity of the human placental GLUT1 glucose transporter, increasing placental glucose transport even in the absence of maternal hyperglycaemia and contributing to macrosomia and other consequences [62].

In the same way, cholesterol and triglycerides increase in maternal plasma throughout pregnancy. Cholesterol is essential for cell proliferation, tissue development and endocrine homeostasis of the growing foetus, and triglycerides are a key energy source for foetal growth and development. The FFAs taken up by the placenta and transported to the foetus originate predominantly from maternal non-esterified fatty acids (NEFAs) and from esterified fatty acids contained in triglycerides (TGs) carried by lipoproteins; the FFAs, after being oxidised in the maternal liver as ketone-bodies, represent an alternative fuel source for the foetus. Maternal TGs have been suggested as the primary source of fatty acids because of their substantial increase in late gestation compared to NEFAs [63].

Some essential fatty acids (EFA) must be obtained from food, since humans and other mammals cannot synthesise them due to the lack of the required desaturase enzymes. Among the EFA, two polyunsaturated fatty acid (PUFA) are very important: alpha-linolenic acid (ALA; with a double bond three carbon atoms, also called omega-3 fatty acid) and linoleic acid (LA; with a double bond six carbon atoms, also called omega-6 fatty acid). Some PUFA (LC-PUFA) of both omega-3 (eicosapentaenoic acid = EPA and docosahexaenoic acid = DHA) and omega-6 type (gamma-linolenic acid = GLA and arachidonic acid = AA) are conditionally essential; e.g. during pregnancy (reviewed in [64]). Mammals have a limited ability to synthesise them and, in case of increased need during gestation, they have to obtain them from food.

During pregnancy, maternal LC-PUFAs are transferred to the foetus, either associated to triglycerides or, in a minor proportion, as FFAs. Selective placental uptake of LC-PUFAs via plasma membrane fatty acid-binding proteins results in higher LC-PUFA concentrations in the foetal than in the maternal circulation. During the last third of pregnancy, AA and DHA are the principal maternal LC-PUFAs. AA determines adequate foetal growth and development but also postnatal metabolism, while DHA is indispensable for the development of the central nervous system and essential for cognitive and visual functions. Both DHA and EPA are important for immune functions. Adequate LC-PUFA supply is also necessary during early postnatal development (i.e. during lactation, [65]).

In case of pregnancies affected by obesity and/or metabolic disorders causing hyperlipidaemia, and usually dyslipidaemia, the foetuses are exposed to high intrauterine concentrations of FFAs and lipids, which also induce accelerated foetal development. During recent years, dietary supplementation of obese pregnant women with PUFAs, mainly omega-3, principally if they develop any component of metabolic syndrome or its complications, has increased in popularity [64,66].

However, the benefit-to-risk ratio of increasing PUFAs intake during pregnancy has not been completely established. It is known that excessive dietary PUFA may – especially in pregnancies with metabolic syndrome or diabetes – have inhibitory effects on desaturase and elongase enzymes, lowering the synthesis of LC-PUFA. Excess dietary PUFAs may also enhance peroxidation and may reduce antioxidant capacity, impairing foetal homeostasis (reviewed in Ref. [66]). Furthermore, the information on the adaptation in placental LC-PUFA metabolism in response to metabolic syndrome is limited and contradictory. Nevertheless, due to the increasing prevalence of nutrition-related diseases (obesity, metabolic syndrome and diabetes), dietary supplementation with PUFA is more widely used, although the risks may

exceed the benefits since the assessment is still scarce. This is therefore a good example of the need for preclinical studies in animal models and, in this sense, lipids metabolism in pregnant females and foetuses are very similar in humans and pigs [67]. The occurrence of disorders like dyslipidemia strongly modifies availability and metabolism of lipids at the fetoplacental unit [68], affecting viability and developmental trajectory of the conceptuses [69].

5. Processes and biomarkers of feto-placental development and IUGR

The adequate supply of nutrients and oxygen to the foetus depends on adequate maternal availability but also on adequate placental transfer. Hence, foetal development depends on efficient placental function. Placental efficiency is primarily determined by its ample development (adequate interdigitation of placenta and endometrium to increase exchange surface, vascular dilation and angiogenesis; [45]), which favours blood flow and exchange of nutrients and oxygen with the conceptus.

Placental insufficiency is currently considered a main factor for pregnancy complications, as described previously [18]. In case of impaired placental function, several placental-secreted proteins, hormones, mRNAs and miRNAs molecules crossing the maternal-foetal barrier may be used as specific biomarkers since they are measurable in the maternal circulation [70–72].

In normal pregnancies, vascular dilation and neoangiogenesis are signalled by proangiogenic factors secreted by the placenta (placental growth factor, PlGF, and vascular endothelial growth factor, VEGF). Vasodilatation and angiogenesis are primarily driven by nitric oxide (NO) and its endothelial constitutive synthase (eNOS or NOS3) which can be found both at the trophoblast, the cells that adhere to and penetrate the uterine endometrium at implantation, and at the extravillous trophoblast, inducing vasodilatation and angiogenesis in maternal cells during the implantation process [73–75]. During the post-implantation period and early placental development, NO and NOS3 are hypothesised to be involved in tissue remodelling, immunosuppression, and vasoregulation [76]. In consequence, a decreased NO bioavailability is recognised to be involved in the pathogenesis of IUGR [77]. Concomitantly, imbalances in the levels of angiogenic regulators, which cause insufficient placental and foetal blood-flow, compromise the supply of oxygen. Insufficient supply of oxygen causes hypoxia and oxidative stress at the feto-placental unit [78]. These facts are also predisposing for cardiovascular disorders at juvenile and adult stages. Overall, these considerations highlight the necessity of adequate biomarkers.

Among the different candidate biomarkers, different authors are addressing the usefulness of asymmetric dimethylarginine (ADMA), an endogenous amino acid derived from proteolytic breakdown of arginine-methylated proteins [79], which by competition with arginine, the substrate of NOS, antagonises the production of NO. ADMA is used in adult individuals with cardiovascular risk and, currently, is being proposed a reliable marker to identify both SGA and LGA subjects at higher risk of health disturbances [80].

This knowledge also provides specific therapeutic targets. There are several amino acids which are precursors of NO; not only arginine but also ornithine, leucine, glutamine, and proline. These amino acids also regulate synthesis of polyamines and proteins; thus, besides favouring placental development and nutrient transfer, also support conceptus development. The results obtained under experimental conditions in swine suggest that amino acids supplementation may be a promising strategy to reduce the incidence of IUGR offspring [81–84], although some of the findings have been conflicting and make necessary further specific studies.

It is well-known that IUGR foetuses are able to modify their metabolic regulation in order to ensure a better use of the scarce nutrients that they have. The mechanism is based on displaying insulin resistance, which allows them to take advantage of the scarce supply of glucose that they are receiving. However, on the other hand, high levels of insulin increase the synthesis of NO inhibitors [85], prejudicing utero-placental blood-flow [86] and reducing the supply of oxygen and nutrients to the foetuses. In fact, IUGR foetuses have a state of low-grade inflammation affecting immune cell proliferation and serum cytokines, as well as an increased susceptibility to infection [87]. In consequence, the use of markers of systemic inflammation, like tumour necrosis factor α (TNFα) and interleukin-6 (IL-6), is also a promising field of study [88].

6. Concluding remarks

The intense research on the causes and mechanisms implicated in the current epidemics of obesity and associated non-communicable disorders has addressed the substantial role of environmental, parental, prenatal and early-postnatal conditions in the development of disease. The individuals, during prenatal and early postnatal development, undertake epigenetic changes in the structure and function of some of their organs and systems. These changes may lead to metabolic disorders at juvenile period and adulthood and may be transferred to subsequent generations by transgenerational inheritance.

The perspective on future research is based on three pillars: the complete understanding of these processes, the availability of contrasted biomarkers for diagnosis and the assessment of preventive and curative treatments. Such research makes necessary interventional procedures, either to affect foetal development and metabolism or to sample the feto-placental unit, which cannot be conducted in humans because of ethical issues.

Hence, preclinical studies in animal models are an important source of biomarker candidates that can be useful for the systematic analysis of pregnancy disturbances and for the efficacy and safety evaluation of new treatments. However, the results need to be translational; hence, the studies have to be performed in adequate animal models. Rodents are the species of election for basic research, but the translational value of large animal models is becoming increasingly recognised in the last years. Further work is however needed to increase the awareness of researchers and medical doctors on the amenability of large animal models. Moreover, the use of large animals implies ethical issues and social repudiation, such that active explanation and promoting of ethical experimentation to the society need to be undertaken.

Acknowledgements

The authors are members of the EU COST-Action BM1308 “Sharing Advances on Large Animal Models (SALAAM)”. More information about SALAAM can be found on the web site: http://www.salaam.genzentrum.lmu.de/.

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