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Developmental Programming of Type 2 Diabetes

Theoretical Background and Experimental Evidence

Oksana H. Zabuha
Oleksandr M. Vaiserman

Chebotarev Institute of Gerontology of the NAMSU, the Academy of Medical Sciences of Ukraine, 67 Vyshgorodska Str., Kyiv 04114, Ukraine

Oksana H. Zabuha
narelem12@gmail.com

Consistent evidence from both theories and experimental studies suggest that inadequate nutrition in early life can contribute to risk for developing metabolic disorders, including type 2 diabetes (T2D) in adult life. Prenatal and/or early postnatal exposures to famine were demonstrated to be associated with higher risk of T2D in many cohorts around the world. Recent studies have highlighted the importance of epigenetic regulation of gene expression as a possible major contributor to a link between an early-life undernutrition exposure and T2D in adulthood. The findings from these studies suggest that a prenatal exposure to undernutrition may result in induction of persistent epigenetic changes that have adaptive significance in postnatal development but can predispose to metabolic disorders including T2D at the late stages of life. In this review, experimental data on the developmental programming of T2D are summarized and recent research findings on changes in DNA methylation that mediate these effects are discussed.

Ключові слова: type 2 diabetes, development, nutrition, experimental model, epigenetics.

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Type 2 diabetes (T2D) is one of the most common chronic diseases constituting a serious social and economic problem in modern societies, both developed and developing. It is caused by insulin resistance resulting from decreased activity and enhanced obesity levels that occur with increasing age. T2D is considered to be adult-onset disease, since it typically occurs in middle-age and old adults. Generally, T2D occurs after the age of 40, although it is now increasingly diagnosed in younger patients [48]. Over the last decades a rapid increase in the prevalence of obesity arising from high caloric diet intake and sedentary lifestyle is driving a global pandemic of T2D. Currently, 415 million people (about 9 % of whole adult population) across the world have T2D. During the next decade, the number of T2D patients is expected to rise to around 642 million persons [22]. Obviously, genetics plays a crucial role in driving this disease, however, the dramatic increase in T2D incidence across the globe cannot be explained by genetic factors alone but must involve environmental factors as well [29]. There is increasing experimental and epidemiological evidence that the risk for development of T2D can be influenced not only by actual adult-life environmental conditions (primarily, lifestyle ones) but also conditions throughout early life [29]. A convincing evidence that risk for T2D cannot be completely attributable to genetic predisposition and/or adult-life environmental factors was obtained, e.g., in a study on Pima Indian nuclear families in which at least one sibling was born before and other after the mother was diagnosed with T2D [9]. In this research, those siblings conceived after the mother has been diagnosed with T2D were 3.7 times more likely to have T2D compared to siblings born before their mother developed diabetes, even though they lived in similar conditions the rest of their lives. In this review there are summarized and discussed findings on the topic from animal model studies.

CONCEPTUAL FRAMEWORK FOR DEVELOPMENTAL NUTRITIONAL PROGRAMMING OF T2D

According to the developmental programming of health and disease (DOHaD) hypothesis, which has been confirmed by many research findings over the past decades, the physiology and structure of the developing organism may be adapted in response to unfavourable environmental conditions, thereby predisposing to many pathological conditions in adult life [13]. In particular, poor nutritional environment in early life can induce structural and functional changes in key organs responsible for nutrient regulation, including brain, liver, adipose tissue, muscle and pancreas [24]. Presently, this view is commonly referred to as the 'predictive adaptive response (PAR)' concept [28]. Exposure to adverse environmental factors such as inadequate or unbalanced nutrient supply during in-utero devel-

opment may long-term 'program' the appetite regulation, feeding patterns, as well as adipose tissue and pancreatic beta cell dysfunction in the developing foetus [29]. As a result of these processes, foetus may be adapted to adverse nutritional conditions by reducing ability to produce insulin and by occurrence of insulin resistance. According to the 'thrifty phenotype' hypothesis [20], such metabolic adaptation may provide short-term survival benefit in poor postnatal environment via the enhanced capacity to store fat in conditions of irregular availability of food resources, but may predispose to the T2D development in conditions of food abundance in postnatal life. More specifically, in malnourished conditions when the foetus exhibits poor growth in utero (commonly referred to as intrauterine growth restriction, IUGR), the foetal adaptation to undernutrition is realized by a variety of mechanisms responsible for the energy and glucose metabolism, such as the enhanced peripheral insulin sensitivity for glucose utilization, increased hepatic glucose production, lowered insulin sensitivity for protein synthesis in muscle, and impaired pancreatic development [43]. All these mechanisms provide obvious survival benefit for the IUGR foetuses by promoting both energy uptake and utilization, reducing the demand for amino acids and anabolic hormones production, and elevating glucose production to maintain glucose supply to vital organs, primarily the heart and brain. These adaptations lead to asymmetrical growth restriction of the foetus, with greatest restriction of muscle and subcutaneous tissue, less of bone, and the least of the brain. Collectively such adaptations allow IUGR foetal tissues to maintain the energy-dependent basal metabolic functions at the expense of body growth in conditions of reduced nutrient supply. If these adaptive modifications persist, or are more readily inducible later in life, they have potential to promote energy absorption beyond metabolic capability when energy supplies increase, thereby causing insulin resistance, obesity and T2D in adulthood [43]. Among the factors affecting the risk of metabolic dysfunctions, including T2D, in adulthood, the prenatal and early postnatal malnutrition (both under- and overnutrition) is currently believed to be most important [7, 41]. It should be noted that in this review only one aspect of malnutrition i.e. undernutrition but not overnutrition will be discussed.

The majority of early population studies used birth weight as a proxy for foetal conditions. From the data obtained, it has been initially concluded that low birth weight is a risk factor for T2D and that birth weight is inversely related to the disease risk [47]. In addition to T2D, low birth weight is a predictor of other T2D-associated conditions and complications later in life, including the impaired body composition and fat distribution [23], fasting lipid profile, blood pressure and insulin resistance [27], life-long activation of the hypothalamic-pituitary-adrenal axis [40], as well as coronary heart disease in adulthood [14]. Several more recent studies, however, found that a relationship between birth weight and risk for T2D is not linear but rather U-shaped, and high birth weight (>4,000 g) is associated with an increased risk of T2D to the same extent as low birth weight (<2,500 g) [21].

An association between low birth weight and risk for T2D in later life is most thoroughly studied to date. This association is apparently mediated by catch-up growth early in life which is an important risk factor for later T2D. The catch-up growth leads to a disproportionately enhanced rate of fat gain in comparison with lean tissue gain [11]. Such preferential catch-up fat is partly driven by mechanisms of energy conservation operating through the suppression of thermogenesis and resulting in the development of thrifty 'catch-up fat' phenotype generally characterized by insulin and leptin resistance. Abnormalities in the growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis, known to play a central role in promoting human growth and development, have been repeatedly reported in children born small for gestational age (SGA) [8]. Such long-lasting abnormalities of IGF-1 in SGA children with catch-up growth are believed to be critically implicated in the association with metabolic disorders, including T2D, later in life.

Precise molecular mechanisms responsible for the nutritional developmental programming of T2D are not yet thoroughly characterized. In many recent studies, compelling evidence was provided that changes in epigenetic regulation of gene expression (heritable alterations in gene function without changes in the nucleotide sequence) is the most plausible mechanism for the link between unfavourable conditions in early development and adverse health outcomes in later life [30]. The main epigenetic mechanisms are DNA methylation and post-translational modifications of histone tails, as well as regulation by non-coding RNAs (microRNAs and long non-coding RNAs) [31]. Evidence for the key role of DNA methylation and other epigenetic mechanisms in mediating the risk of T2D and obesity has been repeatedly documented over the past years [46]. Initial evidence for the role of epigenetic regulation in obesity and T2D has been mainly provided by studies in animal models. These studies reported changes in epigenetic marks in key metabolic tissues following feeding with high-fat diet and by human investigation that demonstrated epigenetic alterations in T2D and obesity candidate genes in obese and/or diabetic persons. More recently, rapid technological advances and price reduction in epigenetic methodologies led to a rapid expansion of epigenome-wide association studies (EWAS) in human epidemiological examinations [46]. These studies clearly demonstrated epigenetic differences between diabetic and healthy control individuals, as well as epigenetic alterations associated with lifestyle interventions.

Within the DOHaD concept, an important point is that throughout embryonic and foetal development, intense epigenetic remodelling takes place that is necessary for the establishment of transcriptional programs responsible for cellular proliferation and differentiation. During these sensitive developmental periods, the epigenome is especially plastic and most sensitive to environmental disturbances [44]. Numerous research findings suggest that early-life adverse events (i.e. insufficient nutrition in utero) might be epigenetically 'imprinted' and 'remembered' decades later, thereby permanently influencing the metabolic phenotype [18]. There is convincing evidence that epigenetic alter-

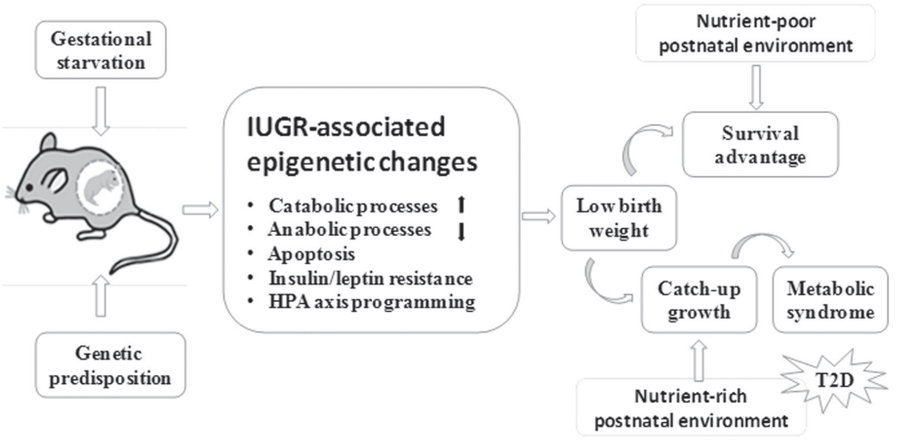

Figure 1. The schematic representation of the hypothetical regulatory pathways responsible for developmental programming of type 2 diabetes (T2D) as a result of an intrauterine growth restriction (IUGR) followed by catch-up growth in nutrient-rich postnatal environment

ations, including those triggered by early-life events and persisted through adulthood, is an important etiological factor in the development of T2D. Changes in DNA methylation and associated changes in patterns of expression of genes implicated in various aspects of glucose metabolism such as β-cell dysfunction, glucose intolerance and insulin resistance, have been shown to be critically involved in the pathogenesis of T2D [1]. The specific DNA methylation markers have been repeatedly identified in peripheral blood and pancreatic islets of the T2D patients (for review, see [25]). A schematic representation of hypothetical regulatory pathways responsible for developmental nutritional programming of T2D is presented in the *Figure* 1.

EVIDENCE FROM ANIMAL MODELS

The bulk of evidence linking intrauterine and/or early postnatal nutrient environment and predisposition to beta-cell failure and T2D in adulthood comes from animal models (for review, see [19, 34, 35]). Most of these studies have used rodent models of 50% maternal dietary restriction (DR) during pregnancy to examine the postnatal beta-cell mass development in pups exposed to either normal or restricted post-natal nutritional conditions. Rodents exposed to intrauterine DR and subsequent normal or restricted post-natal nutrition exhibited diminished beta-cell mass both at birth (30–50 % vs. control) and throughout the early postnatal development (50–70 % vs. control) [12, 15, 16, 33]. In adulthood, these animals were unable to adaptively enhance beta-cell mass in response to rising metabolic demand and consequent insulin resistance. As a result, they have developed diabetic phenotypes characterized by beta-cell failure due to insufficient expansion of beta-cell mass, impaired insulin secretion, glucose intolerance and fasting hyperglycaemia [17, 5]. For example, in a study using cross-fostering methodology to isolate effects of selective pre- and postnatal 50 % DR [26, 42], prenatal DR resulted in a ~50% reduction in beta-cell mass whereas postnatal DR led to decreased body weight, but both beta-cell mass and beta-cell fractional area were increased compared with control animals. These findings indicate that prenatal DR largely determines endocrine cell development while postnatal DR primarily impacts development of the exocrine pancreas [26, 42].

Currently, molecular mechanisms responsible for impaired formation of beta-cell mass in response to early-life DR have come under intensive investigation. Among them, mechanisms of epigenetic regulation of gene activity seem to play a dominant role [30, 37, 38]. Inadequate nutritional environment during intrauterine development suppressed transcription of key genes regulating beta-cell development in rats [37]. Feeding pregnant females with a low-protein diet led to hypomethylation of genes encoding glucocorticoid receptor and peroxisome proliferator-activated receptor gamma in the offspring livers. In a rat model, maternal DR also resulted in a significant reduction in the levels of expression of genes encoding key transcription factors regulating embryonic beta-cell development such as the pancreatic and duodenal homeobox 1 (PDX-1) [4, 32]. Such changes on the epigenetic level were accompanied by reduced postnatal beta-cell formation and incapability to expand beta-cell mass in response to metabolic stress. Moreover, maternal DR diminished the postnatal expression of Pdx-1 gene in pancreatic exocrine ducts which is suspected to harbor a putative pool of pancreatic beta-cell progenitor population in adult rodents [37]. Another factors potentially contributing to these effects are hormones that operate during foetal life, such as insulin, insulin-like growth factors, glucocorticoids, as well as some specific molecules such as taurine [36].

In several studies, maternal protein restriction has been shown to program an insulin-resistant phenotype in rodents, especially in consequence of catch-up growth following intrauterine growth restriction. Such mode of malnutrition resulted in expression of early markers of insulin resistance and metabolic disease risk, including alterations in adipocyte cell size and expression levels of several insulin-signalling proteins through post-transcriptional mechanisms [2]. Catch-up growth following maternal protein restriction also favoured the development of obesity in adult male rat offspring [3]. In a mice model, a protein restriction during foetal life followed by catch-up growth led to obesity in adult male mice [6]. These changes were associated with increased relative fat mass, hypercholesterolemia, hyperglycaemia and hyperleptinemia, and also with altered expression profile of several genes encoding enzymes involved in lipid metabolism.

CONCLUSIONS AND PERSPECTIVES

A trend to a dramatic enhancing incidence of T2D has become a serious problem across the globe over the past years. Metabolic syndrome and associated risk factors including dyslipidaemia, high blood pressure, impaired glucose metabolism and T2D, are among the main causes of death in both developed and developing countries. It is widely believed that risk for T2D is mostly dependent on genetic and life-style factors. However, while genetic factors undoubtedly contribute to an individual susceptibility to development of obesity and T2D, the identified genetic variants can explain only part of the variation [10, 46]. Recent research has demonstrated that exposure to unfavourable environmental factors early in life is another important determinant of the risk of T2D and associated conditions during adulthood. Findings from several of these studies suggest that epigenetic regulation can be largely contributed to development of these pathological states. Since epigenetic marks may persist long-term, epigenetic modifications triggered by environmental cues throughout early sensitive stages may lead to lasting effects on the metabolic functioning, thereby affecting the risk for metabolic disorders, including T2D, later in life [39]. Since epigenetic alterations unlike genetic mutations, are potentially reversible [45], pharmacological modification of epigenetic marks contributing to T2D development can provide a novel approach to prevention and treatment of T2D and associated disorders.

REFERENCES

1. *Alam F., Islam M. A., Gan S. H. et al.* DNA methylation: an epigenetic insight into Type 2 diabetes mellitus // Curr. Pharm. Des. – 2016. – Vol. 22. – P. 4398–4419.

2. *Berends L. M., Fernandez-Twinn D. S., Martin-Gronert M. S. et al.* Catch-up growth following intra-uterine growth-restriction programmes an insulin-resistant phenotype in adipose tissue // Int. J. Obes (Lond). – 2013. – Vol. 37, no. 8. – P. 1051–1057.

3. *Bieswal F., Ahn M. T., Reusens B. et al.* The importance of catch-up growth after early malnutrition for the programming of obesity in male rat // Obesity (Silver Spring). – 2006. – 14, no 8. – P. 1330–1343.

4. *Blondeau B., Avril I., Duchene B., Breant B.* Endocrine pancreas development is altered in foetuses from rats previously showing intra-uterine growth retardation in response to malnutrition // Diabetologia. – 2002. – Vol. 45. – P. 394–401.

5. *Blondeau B., Garofano A., Czernichow P., Breant B.* Age-dependent inability of the endocrine pancreas to adapt to pregnancy: a long-term consequence of perinatal malnutrition in the rat // Endocrinology. – 1999. – Vol. 140. – P. 4208–4213.

6. *Bol V. V., Delattre A. I., Reusens B. et al.* Forced catch-up growth after fetal protein restriction alters the adipose tissue gene expression program leading to obesity in adult mice // Am. J. Physiol. Regul. Integr. Comp. Physiol. – 2009. – Vol. 297, no. 2. – P. R291–299.

7. *Carolan-Olah M., Duarte-Gardea M., Lechuga J.* A critical review: early life nutrition and prenatal programming for adult disease // J. Clin. Nurs. – 2015. – Vol. 24. – P. 3716–3729.

8. *Cho W. K., Suh B. K.* Catch-up growth and catch-up fat in children born small for gestational age // Korean J. Pediatr. – 2016. – Vol. 59. – P. 1–7.

9. *Dabelea D., Hanson R. L., Lindsay R. S. et al.* Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships // Diabetes. – 2000. – Vol. 49. – P. 2208–2211.

10. *Desiderio A., Spinelli R., Ciccarelli M. et al.* Epigenetics: spotlight on type 2 diabetes and obesity // J. Endocrinol. Invest. – 2016. – Vol. 39. – P. 1095–1103.

11. *Dulloo A. G.* Thrifty energy metabolism in catch-up growth trajectories to insulin and leptin resistance // Best Pract. Res. Clin. Endocrinol. Metab. – 2008. – Vol. 22. – P. 155–171.

12. *Dumortier O., Blondeau B., Duvillie B. et al.* Different mechanisms operating during different critical time-windows reduce rat fetal beta cell mass due to a maternal low-protein or low-energy diet // Diabetologia. – 2007. – Vol. 50. – P. 2495–2503.

13. *Eriksson J. G.* Developmental Origins of Health and Disease – from a small body size at birth to epigenetics // Ann. Med. – 2016. – Vol. 48. – P. 456–467.

14. *Frankel S., Elwood P., Sweetnam P. et al.* Birthweight, body-mass index in middle age., and incident coronary heart disease // Lancet. – 1996. – Vol. 348. – P. 1478–1480.

15. *Garofano A., Czernichow P., Breant B.* In utero undernutrition impairs rat beta-cell development // Diabetologia. – 1997. – Vol. 40. – P. 1231–1234.

16. *Garofano A., Czernichow P., Breant B.* Beta-cell mass and proliferation following late fetal and early postnatal malnutrition in the rat // Diabetologia. – 1998. – Vol. 41. – P. 1114–1120.

17. *Garofano A., Czernichow P., Breant B.* Effect of ageing on beta-cell mass and function in rats malnourished during the perinatal period // Diabetologia. – 1999. – Vol. 42. – P. 711–718.

18. *Geraghty A. A., Lindsay K. L., Alberdi G. et al.* Nutrition during pregnancy impacts offspring's epigenetic status - evidence from human and animal studies // Nutr. Metab. Insights. – 2016. – Vol. 8, Suppl 1. – P. 41–47.

19. *Green A. S., Rozance P. J., Limesand S. W.* Consequences of a compromised intrauterine environment on islet function // J. Endocrinol. – 2010. – Vol. 205. – P. 211–224.

20. *Hales C. N., Barker D. J.* Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. 1992 // Int. J. Epidemiol. – 2013. – Vol. 42. – P. 1215–1222.

21. *Harder T., Rodekamp E., Schellong K., et al.* Birth weight and subsequent risk of type 2 diabetes:a meta-analysis // Am. J. Epidemiol. – 2007. – Vol. 165. – P. 849–857.

22. *Jaacks L. M., Siegel K. R., Gujral U. P., Narayan K. M.* Type 2 diabetes: A 21st century epidemic // Best Pract. Res. Clin. Endocrinol. Metab. – 2016. – Vol. 30. – P. 331–343.

23. *Kensara O. A., Wootton S. A., Phillips D. I. et al.* Fetal programming of body composition: Relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen // Am. J. Clin. Nutr. – 2005. – Vol. 82. – P. 980–987.

24. *Kim J. B.* Dynamic cross talk between metabolic organs in obesity and metabolic diseases // Exp. Mol. Med. – 2016. – Vol. 48. – P. e214.

25. *Kwak S. H., Park K. S.* Recent progress in genetic and epigenetic research on type 2 diabetes // Exp. Mol. Med. – 2016. – Vol. 48. – P. e220.

26. *Matveyenko A. V., Singh I., Shin B. C. et al.* Differential effects of prenatal and postnatal nutritional environment on ss-cell mass development and turnover in male and female rats // Endocrinology. – 2010. – Vol. 151. – P. 5647-5656.

27. *Morrison K. M., Ramsingh L., Gunn E. et al.* Cardiometabolic health in adults born premature with extremely low birth weight // Pediatrics. – 2016. – Vol. 138. – pii: e20160515.

28. *Nettle D., Bateson M.* Adaptive developmental plasticity: what is it., how can we recognize it and when can it evolve? // Proc. Biol. Sci. – 2015. – Vol. 282. – P. 20151005.

29. *Nielsen,J. H., Haase T. N., Jaksch C. et al.* Impact of fetal and neonatal environment on beta cell function and development of diabetes // Acta Obstet. Gynecol. Scand. – 2014. – Vol. 93. – P. 1109–1122.

30. *Ong T. P., Ozanne S. E.* Developmental programming of type 2 diabetes: early nutrition and epigenetic mechanisms // Curr. Opin. Clin. Nutr. Metab Care. – 2015. – Vol. 18, no. 4. – P. 354–360.

31. *Paluch B. E., Naqash A. R., Brumberger Z. et al.* Epigenetics: A primer for clinicians // Blood Rev. – 2016. – Vol. 30. – P. 285–295.

32. *Park J. H., Stoffers D. A., Nicholls R. D., Simmons R. A.* Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1 // J. Clin. Invest. – 2008. – Vol. 118. – P. 2316–2324.

33. *Petrik J., Reusens B., Arany E. et al.* A low protein diet alters the balance of islet cell replication and apoptosis in the fetal and neonatal rat and is associated with a reduced pancreatic expression of insulin-like growth factor-II // Endocrinology. – 1999. – Vol. 140. – P. 4861–4873.

34. *Pinney S. E.* Intrauterine growth retardation – a developmental model of type 2 diabetes // Drug Discov. Today Dis. Models. – 2013. – Vol. 10, no. 2. – P. e71–e77.

35. *Portha B., Chavey A., Movassat J.* Early-life origins of type 2 diabetes: fetal programming of the beta-cell mass // Exp. Diabetes Res. – 2011. – Vol. 2011. – P. 105076.

36. *Reusens B., Theys N., Dumortier O. et al.* Maternal malnutrition programs the endocrine pancreas in progeny // Am. J. Clin. Nutr. – 2011. – Vol. 94, 6 Suppl. – P. 1824S–1829S.

37. *Simmons R. A.* Developmental origins of diabetes: the role of epigenetic mechanisms // Curr. Opin. Endocrinol. Diabetes Obes. – 2007. – Vol. 14, no. 1. – P. 13–16.

38. *Simmons R. A.* Developmental origins of adult disease // Pediatr. Clin. North Am. – 2009. – Vol. 56, no. 3. – P. 449–466.

39. *Sterns J. D., Smith C. B., Steele J. R. et al.* Epigenetics and type II diabetes mellitus: underlying mechanisms of prenatal predisposition // Front Cell Dev. Biol. – 2014. – Vol. 2. – P. 15.

40. *Stirrat L. I., Reynolds R. M.* The effect of fetal growth and nutrient stresses on steroid pathways // J. Steroid. Biochem. Mol. Biol. – 2016. – Vol. 160. – P. 214–220.

41. *Tarry-Adkins J. L., Ozanne S. E.* Nutrition in early life and age-associated diseases // Ageing Res. Rev. – 2017. – Vol. 39. – P. 96–105.

42. *Thamotharan M., Shin B. C., Suddirikku D. T. et al.* GLUT4 expression and subcellular localization in the intrauterine growth-restricted adult rat female offspring // Am. J. Physiol. Endocrinol. Metab. – 2005. – Vol. 288. – P. E935–947.

43. *Thorn S. R., Rozance P. J., Brown L. D., Hay W. W. Jr.* The intrauterine growth restriction phenotype: fetal adaptations and potential implications for later life insulin resistance and diabetes // Semin. Reprod. Med. – 2011. – Vol. 29. – P. 225–236.

44. *Vaiserman A.* Epidemiologic evidence for association between adverse environmental exposures in early life and epigenetic variation: a potential link to disease susceptibility? // Clin. Epigenetics. – 2015. – Vol. 7. – P. 9.

45. *Vaiserman A. M.,* Pasyukova E. G. Epigenetic drugs: a novel anti-aging strategy? // Front. Genet. – 2012. – Vol. 3. – P. 224.

46. *van Dijk S. J., Tellam R. L., Morrison J. L. et al.* Recent developments on the role of epigenetics in obesity and metabolic disease // Clin. Epigenetics. – 2015. – Vol. 7. – P. 66.

47. *Whincup P. H., Kaye S. J., Owen C. G. et al.* Birth weight and risk of type 2 diabetes: a systematic review // JAMA. – 2008. – Vol. 300. – P. 2886–2897.

48. *Wilmot E., Idris I.* Early onset type 2 diabetes: risk factors, clinical impact and management // Ther. Adv. Chronic. Dis. – 2014. – Vol. 5. – P. 234–244.

ВІДОМОСТІ ПРО АВТОРІВ

ЛАБОРАТОРІЯ ЕПІГЕНЕТИКИ ІНСТИТУТУ

Вайсерман Олександр Михайлович – керівник лабораторії, д.м.н., професор

Забуга Оксана Геннадіївна – старший науковий співробітник лабораторії, к.м.н.

INFORMATION ABOUT AUTHORS

EPIGENETICS LABORATORY OF THE INSTITUTE

Oleksandr M. Vaiserman, Dr. Sci. (Medicine), Prof., Chief of the Laboratory

Oksana H. Zabuha, Cand. Sci. (Medicine), Senior Research Fellow

РЕЗЮМЕ

Програмування ризику діабету 2 типу: теоретичне обґрунтування та експериментальні дані

Забуга О. Г., Вайсерман О. М.

Державна установа «Інститут геронтології ім. Д. Ф. Чеботарьова НАМН України», вул. Вишгородська, 67, Київ 04114, Україна

Теоретичні дані та й експериментальні дослідження свідчать про те, що недостатнє харчування у ранньому розвитку може підвищити ризик виникнення метаболічних захворювань, включаючи діабет 2 типу (Д2Т) у дорослому віці. Нещодавні дослідження продемонстрували важливість епігенетичної регуляції експресії генів, як можливого основного джерела зв'язку між недостатнім харчуванням упродовж розвитку та Д2Т у дорослому віці. Результати цих досліджень вказують на те, що вплив голоду протягом внутрішньоутробного розвитку може призвести до стійких епігенетичних змін, які, у свою чергу, можуть призвести до адаптаційних рис в організмі вже після народження. Разом із цим, такі епігенетичні зміни можуть спричинити метаболічні порушення, включаючи Д2Т на пізніх стадіях життя. У цьому огляді зведено експериментальні дані щодо можливого «програмування» виникнення Д2Т та узагальнено результати останніх досліджень стосовно змін метилювання ДНК, які опосередковують ці ефекти.

Ключові слова: діабет 2 типу, розвиток, харчування, експериментальні моделі, епігенетика.

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Забуга Оксана Геннадіївна
narelem12@gmail.com

РЕЗЮМЕ

Программирование риска диабета 2 типа: теоретический базис и экспериментальные доказательства

Забуга О. Г., Вайсерман А. М.

Государственное учреждение «Институт геронтологии им. Д. Ф. Чеботарёва НАМН Украины», ул. Вышгородская, 67, Киев 04114, Украина

Теоретические данные и экспериментальные исследования показывают, что недостаточное питание в раннем возрасте может способствовать риску развития метаболических нарушений, включая диабет 2 типа (Д2Т) во взрослом возрасте. Недавние исследования подтвердили важность эпигенетической регуляции экспрессии генов, как возможного главного связующего фактора между недостаточным питанием при раннем развитии и Д2Т во взрослой жизни. Результаты этих исследований показывают, что пренатальное воздействие голода может привести к индукции постоянных эпигенетических изменений, которые имеют адаптивное значение в организме на постнатальном этапе развития, но могут и предрасполагать к нарушениям обмена веществ, включая Д2Т на поздних стадиях жизни. В этом обзоре обобщены экспериментальные данные относительно программирования развития Д2Т и обсуждаются последние результаты исследований изменений метилирования ДНК, которые опосредуют эти эффекты.

Ключевые слова: диабет 2 типа, развитие, питание, экспериментальные модели, эпигенетика.

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