MedCrave
Step into the World of Research

Endocrinology & Metabolism International Journal

Mini Review

Open Access

CrossMark

Translational and some other aspects of DOHaD concept: a polemic overview related to endocrinology and public health

Abstract

This mini-review describes translational, historical and some other aspects of the concept of developmental origins of health and disease (DOHaD), as well as the connection between development and aging as a challenge to DOHaD paradigm. The main focus is made on endocrine and metabolic mechanisms studied by means of experimental models of laboratory animals and cell cultures and on epidemiological indices of morbidity and mortality in human populations. It is concluded that future investigations should be directed to enforcing the links between biomedical and public health implications of research in DOHaD area.

Keywords: endocrine mechanisms, translational research, development, aging, morbidity, mortality

Volume 11 Issue 1 - 2023

Goudochnikov VI
Department of Biochemistry, Member of ISOAD, Brazil

Correspondence: Goudochnikov VI, Department of Biochemistry, Member of ISOAD, Rua Matoso Camara 73, Bairro Menino Jesus, CEP 97050-500, Santa Maria-RS, Brazil, Tel +5555991310805, Email victori40@hotmail.com

Received: February 14, 2022 | **Published:** February 23, 2023

Abbreviations: CRF/CRH, corticotropin-releasing factor/hormone; DHEA, dehydroepiandrosterone; DOHaD, developmental origins of health and disease; GC, glucocorticoids; HPA, hypothalamic-pituitary-adrenal; SGA, small for gestational age

Introduction

Approximately 30 years ago, in 1992 the author of this essay heard the following phrase of a Japanese economist: "If you don't recognize a problem, then, obviously, you cannot resolve it". So we shall try here to recognize the problems that are on a horizon for researchers involved in DOHaD paradigm, focusing on endocrine mechanisms and public health implications.

At first, we shall affirm that during this period of time the so called "Barker's hypothesis" has transformed to DOHaD concept accepted in a world-wide mode,[1] although a lot of not so simple questions have emerged. Considering also that basically, DOHaD paradigm is composed of two principal branches, epidemiological and biomedical, we shall discuss at first, if studies on the mechanisms of programming/imprinting phenomena, when performed by using experimental models on laboratory animals, can help in the interpretation of data obtained in human populations.

Translational aspects of DOHaD concept

Many investigations exploring the role of glucocorticoids (GC) in programming/imprinting phenomena, were made on rats, using low protein diet in pregnancy. However, the rate of protein utilization in rats is about 23-fold higher, as compared to humans, therefore the impact of this diet in rats should be much greater. Moreover, rats have approximately 10 fetuses, with their total relative mass much higher, as compared to human gestation.[2-4]

In addition, we should comment here that the impact of low protein diet during pregnancy may have various underlying mechanisms, with possible modification of the levels of many hormones besides GC (see also the sections "Final comments" and "Notes added in proof" at the end of the article for more details).

Another important difference between humans and rats is the rate of maturation in perinatal period. As a result, neonatal rats correspond to human fetuses in the 3rd trimester of pregnancy or (even better) to preterm human infants.[5] On the other hand, rat fetuses on the 3rd week of gestation appear to correspond to human fetuses in the 2nd trimester of pregnancy,[6] whereas rats at the end of 2nd postnatal week appear to correspond to one-year old human infants.[7]

In any case, our attempts to perform the periodization of postnatal ontogeny in humans and rats on the basis of linearization of somatic growth curves by means of using mono- and bilogarithmic plots have demonstrated juvenile and pubertal transitions as the breaks of continuous straight lines both in humans and rats. However infantile transition was observed only in humans.[8,9] It is interesting that in rats juvenile and pubertal transitions separate postnatal ontogeny to 3 phases (or stages) that roughly correspond to the periods of development with different mechanisms of tissue growth:[10]

A. predominant hyperplasia;

B. combined hyperplasia and hypertrophy;

C. predominant hypertrophy.

However, we were greatly disappointed to find out an investigation showing 3 similar phases in prenatal ontogeny also.[11] Moreover, infantile transition in humans at the age of 1-2years appears to correspond roughly to weaning that occurs in rats at the end of 3rd postnatal week, when juvenile transition takes place in this species.

Earlier we have launched an idea that at least in humans juvenile transition corresponds to metamorphosis-like process occurring at the age of 6-8years, close to inversion of the curve of total mortality in human populations for both genders at the age of 9-10years. In contrast, pubertal transition takes place in girls 2years earlier than in boys (at the ages of 12 and 14years respectively).[10] If to consider aging as a process that provokes increasing morbidity and mortality, then on our opinion, juvenile transition corresponds better than pubertal one to general transformation from development to aging.

It is important that pubertal transition with menarche in girls is subjected to secular trend, with a tendency to occur in earlier age than in the past. On the other hand, juvenile transition, with a landmark of a change from deciduous to permanent teeth, still awaits the attention of researchers, including the specialists in odontology and anthropology.

Approximately 30 years ago we have offered a theoretical model of adenohypophyseal cytodifferone, and recently this model was updated, proposing a similar construct for adrenal cortex.[10] It is important that in both models infantile transition appears to correspond to adrenocortical maturation, whereas juvenile and pubertal transitions correspond to thyroid and gonadal maturation respectively, and all these transitions appear to correspond to drastic changes of environment for early vertebrates:

A. from salty water of oceans and seas to salt less water of rivers and lakes;

B. to coastal land near the last;

C. to the land far away from the coast.

In any case, the invertebrate species don't possess the enzymes of biosynthesis and receptors for GC[12] that are considered as principal candidates for hormonal mediators and targets of programming/imprinting phenomena.[13] Probably, in at least some species of invertebrates the central components of hypothalamic-pituitary-adrenal (HPA) axis are involved in such phenomena, together with interleukins and other cytokines.

Of course, we are aware of highly hypothetical nature of these theoretical constructs, but we hope that they may serve at least as a starting point for further discussions, models and concepts.

Historical and some other aspects of DOHaD concept

It is obvious to us that earlier works in DOHaD paradigm were related in great part to nutrition aspect. Therefore, it is understandable that the first use of the term "programming" was attributed to Lucas in relation to altered human nutrition in early postnatal period.[14] However, as a matter of fact, Swedish biochemist Jan Ake Gustafsson was the first to employ the term "programming" already in 1972-1974, as referred to organizational effects of sex steroid hormones in rats.[15]

Moreover, it was affirmed that before David Barker, German researcher Gunter Dorner has performed a series of studies on sexual differentiation of the brain in a mode, quite close to DOHaD paradigm. Nevertheless, only after the continuous investigations of David Barker and his colleagues and followers, the DOHaD concept was rather firmly established in a world-wide mode.[1]

Our first studies related to DOHaD paradigm were performed at the end of eighties of the last century, in parallel to seminal works of David Barker and his collaborators, although this relationship was recognized by us only at the beginning of the current century. In fact, comparing primary cultures of liver cells obtained from fetal and prepubertal rats, we have observed high sensitivity of hepatocytes to various hormones, especially to GC, already in late prenatal period.[16]

Somewhat later on, we have repeated age-related comparisons on primary cultures of pituitary cells obtained from neonatal, prepubertal and adult rats, also showing high sensitivity to hormones including GC already in neonatal period. Really, in some cases such sensitivity was even higher than in cultures of more mature animals.[17,18] On the basis of these data we have concluded that GC, together with some other hormonal bioregulators can indeed participate as mediators in programming/imprinting phenomena during perinatal period of ontogeny.

Finally, our studies in vivo have demonstrated higher sensitivity of rats to GC-induced inhibition of somatic and organ growth especially in neonatal period.[19] Moreover, later we have shown the capacity of GC to decrease the extent of tissue hydration, as a possible mechanism of GC accelerating action on body maturation and cell differentiation, as well as their inhibitory influence on cell proliferation.

However, we should also take account of interspecies differences, as related to GC. In fact, rats and mice, hamsters and rabbits are highly sensitive to GC, whereas guinea pigs and some primates like marmoset monkeys, as well as humans are relatively resistant to them.[20-24] In part, these differences may be explained by lower affinity of GC receptors in GC-resistant species.[25]

Moreover, there exist interspecies differences in hormonal regulation during pregnancy. For example, rats don't possess placental corticotropin-releasing factor/hormone (CRF/CRH), in contrast to humans. On the other hand, in humans and other primates estrogens are synthesized from fetal dehydroepiandrosterone (DHEA) at the end of pregnancy, whereas in rats they are produced by the ovaries.[26,27]

At last, it is not clear, why stress or GC in excess during prenatal period provoke higher GC levels in adult offspring, whereas GC in neonatal period, on the contrary, cause their decrease.[28,29] By the way, relative significance of stress and GC in small for gestational age (SGA) and preterm birth is not clear yet.[30-32]

Connection between development and aging: An underserved part of DOHaD paradigm

The data obtained in epidemiological studies of David Barker and many other researchers have clearly shown that programming/imprinting phenomena can provoke life-long consequences till the senescence in humans, especially as referred to higher risk of cardiometabolic disorders. Nevertheless, our results of analyzing the relative (or proportional) morbidity and mortality in various populations of Brazilian Southern region, as well as Argentina and Chile have clearly demonstrated rather high heterochronicity in various groups of disorders.[33-35]

For example, in contrast to cardiometabolic disorders, characteristic to advanced age categories (60-80years), schizophrenia and affective disorders, peptic ulcer and cholecystitis had the maxima of morbidity in the intermediate age groups (30-50years). Moreover, there were clear gender differences, for example schizophrenia and peptic ulcer were predominant in males, whereas affective disorders and cholecystitis were more characteristic to females.

Finally, with the onset of menopause at the age of about 50years, age-related female fraction of relative morbidity and mortality has shown a steady increase that was interpreted by us as indicator of accelerated aging in climacteric females.[36] Just recently we have confirmed this peculiarity on the populations of Argentina and 3 European countries (France, Spain and UK), using the data retrieved from the WHO database of mortality.[37]

Analyzing all these results, we have concluded that there is no evidence in favor of unique general scheme of aging,[33] if to assume the definition of aging as biological process provoking the increases in morbidity and mortality with advancing age, clearly dependent also on human gender.

Trying to apply these results to the discussion of proposals about primary roles of GC and stress in programming/imprinting and embedding phenomena, we supposed that age-related tendency to hypercortisolism can explain, at least partially, the age-related dynamics and perhaps, even sexual dimorphism of epidemiological indices. But in order to do it, we had to assume the interactions of GC with other hormones possessing anti-stress properties, first of all melatonin, growth hormone, estrogens and weak adrenal androgens,

the levels of which appear to demonstrate characteristic age-related decreases.[38]

Final comments

In conclusion, translational and some other aspects of DOHaD concept pose serious challenges for researchers involved in DOHaD paradigm. On our opinion, one of the problems really difficult to resolve at present is trying to interprete the capacity of GC to provoke programming/imprinting phenomena in early gestation, when hormonal mechanisms are immature yet. Although it is quite clear that in these cases GC action can be indirect one, being mediated by placenta and its hormones, nevertheless some rather scarce data have already demonstrated the ability of GC and other hormones to influence, for example, human induced pluripotent stem cells, close in their immaturity to embryonic stem cells.[39]

Both David Barker and some later followers of DOHaD concept have outlined the principal its intention to promote better health and well-being for future human generations.[40] From our part, we hope that one of the principal aims of biomedical specialists, as referred to DOHaD paradigm, should be better control of exposure to stress and GC excess, especially in perinatal period,[5,41] because of essential role of GC, in combinations with other hormones, in the phenomena of programming/imprinting.[42,43]

Notes added in proof

For obtaining more data, the interested readers are addressed to our numerous articles in open access journals about the roles of GC and various other bioregulators including hormones, cytokines, etc., as well as their interactions in the ontogeny. The majority of them are mirrored on the author's personal pages of ResearchGate and Academia websites and are cited in ORCID register, with the links to original publications. Undoubtedly, one of the most interesting aspects concerns the interactions of GC with thyroid hormones, both in development and aging.

Acknowledgments

The author is grateful to various members of International Society for DOHaD for their kind attention during his participation in its Council (2011-2019), as well as in its Latin-American Chapter (2009-2020).

Conflicts of interest

The author declares that conflicts of interest do not exist.

Funding

None.

References

1. Rabadan–Diehl C, Nathanielsz P. From mice to men: Research models of developmental programming. *J Dev Orig Health Dis*. 2013;4(1):3–9.
2. Morley R, Dwyer T. Fetal origins of adult disease? *Clin Exp Pharmacol Physiol*. 2001;28(11):962–966.
3. Gopalakrishnan GS, Gardner DS, Rhind SM, et al. Programming of adult cardiovascular function after early maternal undernutrition in sheep. *Am J Physiol Regul Integr Comp Physiol*. 2004;287(1):R12–R20.
4. Morley R. Fetal origins of adult disease. *Semin Fetal Neonat Med*. 2006;11(2):73–78.
5. Goudochnikov VI. Perinatal treatment of some respiratory disorders with glucocorticoids in relation to prematurity. *EC Pulmonol Respir Med*. 2017;6(1):23–27.
6. Koenig JI, Elmer GI, Shepard PD et al. Prenatal exposure to a repeated variable stress paradigm elicits behavioral and neuroendocrinological changes in the adult offspring: Potential relevance to schizophrenia. *Behav Brain Res*. 2005;156(2):251–261.
7. Avishai–Eliner S, Brunson KL, Sandman CA, et al. Stressed–out, or in (utero)? *Trends Neurosci*. 2002;25(10):518–524.
8. Goudochnikov VI, Prokhorov LY. The phases related to somatic growth in postnatal ontogenesis, as refered to transition between development and aging. In: 1st European Congress of Biogerontology. Helsingor, 1998, p.80
9. Goudochnikov VI, Prokhorov LY. Linearized non–monotonic growth plots reveal ontogenetic transitions probably related to principal transformation from development to aging. *Adv Med Biol*. (New York) 2020;170:227–238.
10. Goudochnikov VI. Metamorphosis–like process in ontogeny: Possible mechanisms and association with transition from development to aging. *Journal of Gerontology and Aging Research*. 2017;1(1):103.
11. Shalitin S, Lebenthal Y, Phillip M. Children born small for gestational age: Growth patterns, growth hormone treatment and long–term sequelae. *Isr Med Assoc J*. 2003;5(12):887–882.
12. Goudochnikov VI. Evolution of stress hormones and proteins in relation to developmental origins of health and disease. *Integrat Mol Med*. 2019;6:1–3.
13. Reynolds RM. Nick Hales Award Lecture 2011: Glucocorticoids and early life programming of cardiometabolic disease. *J Dev Orig Health Dis*. 2012;3(5):309–314.
14. Singhal A, Lucas A. Early origins of cardiovascular disease: Is there a unifying hypothesis? *Lancet*. 2004;363(9421):1642–1645.
15. Goudochnikov VI. Paradigm of DOHaD in historical perspective: A personal view. In: DOHaD ANZ Digital Trainee Conference, 2020.
16. Baranova IN, Gudoshnikov VI, Fedotov VP. Hormonal regulation of serum albumin production by pre– and postnatal rat hepatocytes in culture. *Bull Exp Biol Med*. 1990;109(6):777–780.
17. Gudoshnikov VI, Fedotov VI. The heightened sensitivity of hypophyseal cells of neonatal rats to corticosteroids. *Neurosci Behav Physiol*. 1993;23(2):107–111.
18. Gudoshnikov VI, Fedotov VP. Increased sensitivity of neonatal rat pituitary cells to bromocriptine and melatonin. *Bull Exp Biol Med*. 1993;115:202–204.
19. Goudochnikov VI. Pathogeny of glucocorticoid–induced growth retardation evaluated in experimental studies using laboratory animals and cell cultures as the models. *NewsLab (Sao Paulo)*. 1997;22:90–100.
20. Claman HN. Corticosteroids and lymphoid cells. *N Engl J Med*. 1972;287(8):388–397.
21. McEwen BS, Biron CA, Brunson KW et al. The role of adrenocorticoids as modulators of immune function in health and disease: Neural, endocrine and immune interactions. *Brain Res Rev*. 1997;23(1–2):79–133.
22. Dean F, Yu C, Lingas RI, et al. Prenatal glucocorticoid modifies hypothalamo–pituitary–adrenal regulation in prepubertal guinea pigs. *Neuroendocrinology*. 2001;73:194–202.
23. Hauser J, Dettling–Artho A, Pilloud S, et al. Effects of prenatal dexamethasone treatment on postnatal physical, endocrine, and social development in the common marmoset monkey. *Endocrinology*. 2007;148(4):1813–1822.
24. Hauser J, Knapman A, Zurcher NR, et al. Effects of prenatal dexamethasone treatment on physical growth, pituitary–adrenal hormones, and performance of motor, motivational, and cognitive tasks in juvenile and adolescent marmoset monkeys. *Endocrinology*. 2008;149(12):6343–6355.

25. Owen D, Matthews SG. Repeated maternal glucocorticoid treatment affects activity and hippocampal NMDA receptor expression in juvenile guinea pigs. *J Physiol*. 2007;578(pt 1):249–257.

26. Burton PJ, Waddell BJ. Dual function of 11 beta–hydroxysteroid dehydrogenase in placenta: Modulating placental glucocorticoid passage and local steroid action. *Biol Reprod*. 1999;60(2):234–240.

27. Hobel C, Culhane J. Role of psychosocial and nutritional stress on poor pregnancy outcome. *J Nutr*. 2003;133(5–Suppl 2):1709S–1717S.

28. Reynolds RM, Phillips DIW. Long–term consequences of intrauterine growth retardation. *Horm Res*. 1998;49(Suppl 2):28–31.

29. Kamphuis PJGH, Bakker JM, Broekhoven MH. Enhanced glucocorticoid feedback inhibition of hypothalamo–pituitary–adrenal responses to stress in adult rats neonatally treated with dexamethasone. *Neuroendocrinology*. 2002;76(3):158–169.

30. Hauser J, Feldon J, Pryce CR. Prenatal dexamethasone exposure, postnatal development, and adulthood prepulse inhibition and latent inhibition in Wistar rats. *Behav Brain Res*. 2006;175(1):51–61.

31. Kaijser M, Bonamy A–K, Akre O, et al. Perinatal risk factors for ischemic heart disease: Disentangling the roles of birth weight and preterm birth. *Circulation*. 2008;117(3):405–410.

32. Pluess M, Belsky J. Prenatal programming of postnatal plasticity? *Dev Psychopathol*. 2011;23(1):29–38.

33. Goudochnikov VI. Comparison of age–related dynamics and gender differences in morbidity and mortality caused by several groups of diseases: No evidence for unique general scheme of aging potentially modifiable by perinatal programming. *J Dev Orig Health Dis*. 2009;1:S123.

34. Goudochnikov VI. Direct comparisons of relative morbidity caused by various disorders in the population of Chile and one of Brazil's southern states. *J Dev Orig Health Dis*. 2017;8:S448.

35. Goudochnikov VI. Direct comparisons of relative mortality caused by various disorders in the populations of Argentina and southern region of Brazil. *J Dev Orig Health Dis*. 2017; 8: S448–S449.

36. Goudochnikov VI, Prokhorov LY. Accelerated aging with the onset of menopause: Possible connection to hormonal changes and stress proteins. *Probl Star Dolgolet (Kiev)*. 2012;21:274–279.

37. Goudochnikov VI. International comparisons of mortality from cardiometabolic diseases in the ontopathogenic model. In: 22. Congresso Brasileiro de Geriatria e Gerontologia. Evento Online; 2021.

38. Goudochnikov VI. Role of hormonal regulation and stress in the interaction of sleep and biorhythms in aging. *Adv Gerontol*. 2014;27(1):44–49.

39. Goudochnikov VI. Glucocorticoid–induced growth inhibition: An update. *J Endocrinol*. 2022;6(1):000165.

40. Barker DJP. Low birth weight, early growth and chronic disease in later life. *Pediatric Basics*. 2003;104:12–20.

41. Goudochnikov VI. Stress in different periods of ontogeny: Consequences and peculiarities. *Global J Med Res*. 2020;20(A3):9–11.

42. Goudochnikov VI. Role of hormones in perinatal and early postnatal development: Possible contribution to programming/imprinting phenomena. *Russ J Dev Biol*. 2015;46(5):237–245.

43. Goudochnikov VI. Central positions of glucocorticoids and stress in the phenomena of hormonal and metabolic programming/imprinting. *J Endocrinol Sci*. 2023;5(1):1–7.