Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Annals of Biological Research, 2012, 3 (4):1866-1870
(http://scholarsresearchlibrary.com/archive.html)

Annals of Biological Research
Scholars Research Library
ISSN 0976-1233
CODEN (USA): ABRNBW

Developmental plasticity and programming of cardiovascular function in prevention of genetic hypertension

Anna Zemančíková, Jozef Török, Marcela Tabačeková

Institute of Normal and Pathological Physiology, Slovak Academy of Sciences, Bratislava, Slovak Republic

---

ABSTRACT

It is becoming increasingly clear that the genetically determined program of an organism is modified in response to variable environmental conditions operating during its development. Experimental results from animal studies as well as clinical data indicate that especially the prenatal and early postnatal events can initiate long-term changes in the expression of the genetic program which persist, or may only become apparent, later in the individual's life. The effects of early-life events are often viewed in light of pathology, as they can increase the risk for a particular disease. But alternatively, the knowledge concerning developmental plasticity may be effectively utilized in targeted programming of phenotypic properties in effort to prevent the manifestation of particular disease state in subjects with significant genetic predisposition. This review describes some of the basic mechanisms of developmental plasticity and its possible application in pharmacological prevention of hypertension development in young individuals genetically predisposed to high blood pressure.

Key words: developmental plasticity; hypertension; ontogenesis; spontaneously hypertensive rat.

INTRODUCTION

Developmental plasticity as a general adaptive phenomenon in biological systems: An introduction

Phenotypic plasticity is considered as a general adaptive phenomenon in biological systems reflecting the capacity of a particular set of genes to give rise the different phenotype variants in response to variable environmental conditions. It partially results from the fact that all biological processes are directly subjected to physical and chemical laws of the nature. On the other hand, it may facilitate the evolution of adequate reactions to an actual or expected changes, to regular or irregular variability of the environment [1].

If the phenotypic plasticity is studied in developmental context, it may be denoted as developmental plasticity. Generally, it is related to irreversible alterations in gene expression that occur within particular sensitive periods in ontogenesis, as a consequence of perception and integration of specific information from the environment [2, 3]. On the level of the cell, they can permanently influence its functional settings and may be transferred to its posterity. Several mechanisms on the molecular level are proposed to be the basis of the described processes, including covalent and noncovalent modifications of DNA and histone proteins, which influence higher levels of chromatin structure and thereby also the expression of the respective part in DNA [4, 5]. At the present time, these are the subject of intensive research – also in connection with specific developmental abnormalities or with the origin of some human multifactorial diseases that represent the consequences of adverse interactions between the genome and the environment during early ontogenesis of an individual [4, 6].

From the mentioned facts it follows that one particular genotype can produce several phenotype variants (without changes in the primary structure of DNA) and that the presence of particular environmental signals in time and space is critical for this. The level of plasticity in the given organism as well as its time localization and duration

within ontogenesis may be highly variable, dependent on the species, on the environmental factor studied or the respective phenotypic trait [3]. It is possible to demonstrate it on a very general example in biology, which is related to the striking differences in ontogenetic processes in plants and animals. These two groups of organisms evolved from the unicellular ancestor; their evolutionary paths to multicellular forms presumably progressed independently from each other and reflect their different life strategies [7]. Due to the existence of meristematic tissues, plants have very specific manner of growth and development characterized by considerable flexibility. Extreme developmental plasticity is evident from the number, shape and function of organs until to the level of individual cells, where it is expressed in the low degree of determination in their differentiation. The plant cells, even though being highly specialized, are characterized by the reversibility of differentiated state and the ability to change their developmental program, which can be associated even with the induction of embryogenic processes (somatic embryogenesis) during extreme conditions. It reflects the unique property of plant cell – totipotency, i.e., the capability to utilize its whole genetic potential as necessary, depending on the actual environmental conditions [8]. It is supposed that such plasticity in developmental processes is a compensation for the restricted possibilities in locomotion and behaviour manifestation in plants [9].

By contrast, in most of the animals, the grounds of tissues and organs are established definitely in the early ontogenesis and, especially in higher vertebrates, the processes of cell differentiation, tissue and organ formation are under stricter control of the genome. Even though, the interaction between the genome and the environment plays very important role during animal growth and development. It seems, however, that the susceptibility of developmental processes to be radically affected by environmental factors is mostly concentrated into particular limited periods of early ontogenesis (developmental windows), when intensive cell growth and functional specialization (determination of gene expression profile) in particular tissues/organs occurs. During these sensitive stages, most of functional systems in an organism changes from open to closed regulation circuits which are controlled by many feedback mechanisms. The actual value of a given physiological parameter is fixed as the „set point“ – required value of the regulated system, which then determines its functioning through the whole life. Changes in some components/aspects of the environment during these periods may therefore markedly influence the setting of physiological functions [10].

Epigenetics in etiological context of multifactorial disorders

The results from animal experiments as well as observations in humans show that environmental influences in early ontogenesis may have substantial impact on the health and fitness of an individual as they can lead to extensive and permanent modifications in its physiology and morphology [11]. In some instances, these alterations lead to the origin of various pathological stages like some metabolic, cardiovascular, autoimmune, oncogenous, neurobehavioral, respiratory or reproductive diseases, in which the significant degree of epigenetic determination is proposed [12-14]. The exact etiology of these disorders, however, remains still largely unknown.

It has become evident that the developmental processes are strongly influenced by the action of stress hormones. Stressful intrauterine environment (e.g. during malnutrition of the maternal organism or hypoxia) may cause fetal growth restriction and premature birth [15, 16]. Timing of birth is controlled by the concentration of hypothalamic corticoliberin (corticotropin-releasing hormone, CRH) and adrenal steroids in fetus; maternal corticoids and CRH of placental origin may also be of great importance [17, 18]. Intrauterine stress induces an early maturation of hypothalamic-pituitary-adrenal axis whose hormonal components strongly interfere with the developmental processes: they accelerate the tissue and organ maturation (brain and lungs; [19]) at the expense of the growth processes to ensure the survival of the prematurely born neonate. These reactions have an adaptive character in terms of individual’s survival during its early development; however, they can also have negative influence on its health state later in life [20, 21].

The increase in basal concentration of CRH in the paraventricular nucleus and plasmatic concentration of corticosteroids in fetus, fixed by the long-term prenatal or neonatal stress, is often connected with hyperphagia and rapid weight gain in the early postnatal life („catch-up growth“) [22]. Despite of this compensation in the body growth, such prenataly stressed individuals have greater predisposition to development of some disorders in adulthood, as hypertension, obesity or diabetes mellitus type 2 [20, 22]. The combination of the low body weight at birth and its fast postnatal increase rather multiply the incidence of these pathological states. In an effort to clarify the mechanisms of these developmental abnormalities and to reveal their real adaptive value, several authors have tried to elaborate the theory of the fetal programming of physiological functions [13, 23] and the terms like „thrifty phenotype“ [24, 25] and „predictive adaptive response“ [12] were coined. In this model, the developing organism responds to the unfavourable conditions by the growth reduction and by the permanent setting of its physiology on such level which corresponds to the anticipated (nutritional) deprivation in its postnatal life. However, if the real conditions of the postnatal environment are markedly different from the expected state (e.g. at high nutritional supply), the risk of the origin of the aforementioned disorders rapidly increases [12]. Such a view on the

etiopathogenesis of the majority of human multifactorial diseases also offers new possible approaches in their prevention, diagnostics and therapy.

The knowledge concerning developmental plasticity and programming of phenotypic properties may be further effectively utilized in prevention of disease development in individuals with significant genetic predisposition. It means that the proper intervention (nutritional, pharmacological, behavioral) applied during the early ontogenesis can lead to such a setting of the structural and functional parameters which may decrease the clinical manifestation of the genetically determined pathological state later in life. This may also raise the quality or length of life in such individual. The described idea of phenotype modeling supposes the detail knowledge of developmental biology of the studied object with focus on its early ontogenetic processes and on their alterations in individuals pre-determined to the development of the specified disease.

Prevention of genetic hypertension development by pharmacological intervention during early ontogenetic stages

Essential hypertension is a typical multifactorial disease in which the interaction between susceptibility genes and environmental factors is intensively studied [26]. Several animal models with genetic predisposition to hypertension are used for this purpose. Particularly utilized is the model of spontaneously hypertensive rats (SHR), as the pathogenesis of hypertension in these animals has several common traits with human essential hypertension [27, 28]. In young rats with developing spontaneous hypertension, the parallel increase in the arterial resistance and cardiovascular hypertrophy are observed, which are most intensive just during the phase of the rapid increase in blood pressure that is situated into the period between 4th and 10th week of their life. It is assumed that the proper antihypertensive treatment during this developmental phase of SHR may have preventive effect not only on the pathological elevation of their blood pressure but also on the hypertrophic processes in the cardiovascular system. One can expect that in older animals with established hypertensive disease it is rather difficult to induce the regression of structural alterations in the heart and vessel system that have developed as a consequence of long term influence of increased blood pressure on the cardiovascular system [28, 29].

Recently, we have studied the effectiveness of various antihypertensive substances in two early phases of hypertension development in SHR. The selected drugs were administered to these rats during the period between 4th and 8th week (early phase of rapid blood pressure elevation) and between 8th and 12th week (late phase of rapid blood pressure elevation) of their life.

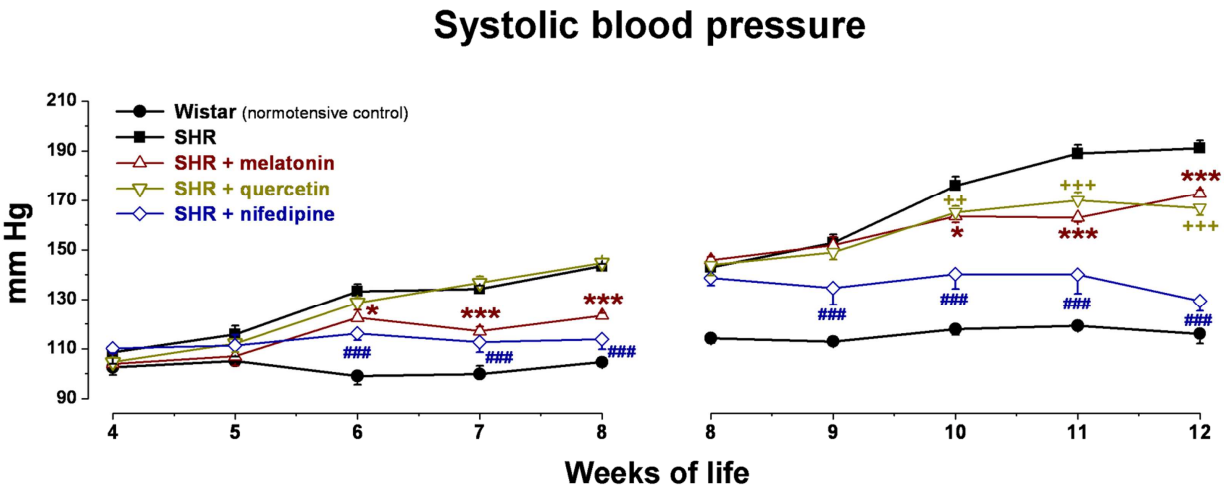

Figure 1. Effect of treatment with various blood pressure-decreasing substances – melatonin, quercetin, and nifedipine – on blood pressure elevation during two stages of hypertension development in spontaneously hypertensive rats (SHR). ∗ P<0.05; ++ P<0.01; ∗∗∗(+++)(###) P<0.001 *vs.* SHR

Figure 1 shows that melatonin – an endogenous hormone involved in the circadian regulation in mammals (which has also an important blood pressure-decreasing effect) – when applied exogenously in pharmacological doses, it partially prevented hypertension progress in both age groups of rats. The magnitude of its effect was very similar to that observed in established hypertension [30]. The finding that antihypertensive effect of melatonin treatment is not more pronounced when applied during the earlier stages of hypertension development in SHR may be related to the

fact that in juvenile rats the endogenous melatonin production is probably higher than in the older group [31]; this can avoid the more intensive action of melatonin added exogenously into the young organism.

The another substance used was quercetin, a natural plant flavonoid mostly known for its potent antioxidant properties. In our experiments, it did not influence the development of hypertension in its very early stage but significantly decreased blood pressure increment when applied to the older group of SHR, in which hypertension was already partially evolved (Figure 1). The concentration of conjugated dienes in left ventricle tissue, as a marker of oxidative damage, was also reduced only in SHR treated between 8^{th} and 12^{th} week of life [32]. Considering predominantly the free radical-scavenging action of quercetin, we can indirectly presume from our results that the higher production of reactive oxygen species may not play a role in initiation of hypertension in SHR but it may contribute to its further progression in later ontogenesis.

The most considerable effect in prevention of pathological blood pressure increase in SHR was seen during the treatment with nifedipine, one of the dihydropyridine calcium channel blockers, representing an important group of drugs frequently used in the therapy of human hypertensive states. We found that in both examined stages of hypertension development, nifedipine prevented the elevation of blood pressure over its initial levels, the percentual decrease of blood pressure values being slightly more pronounced when it was administered to rats between 8^{th} and 12^{th} week of age, i.e., when their blood pressure was already pathologically increased (Figure 1). In this older group of SHR, nifedipine was also more effective in amelioration of vascular function, which was evident from our *in vitro* measurements [33]. These results partly confirm the findings of other authors which demonstrated that the antihypertensive effect of dihydropyridine calcium antagonists is in the positive correlation with the initial level of blood pressure, which is directly related to the level of membrane potential and to the function of voltage-dependent calcium channels in vessel smooth muscle cells [34].

These observations suggest that various hypotensive drugs, which are successfully used in the treatment of established hypertension (in experimental as well as in clinical conditions), may not be equally effective when applied during the process of early blood pressure elevation in young individuals with developing hypertension. Certainly, this effect is largely dependent on the way of their action and it is possible to use this experimental design to explore which regulatory mechanisms are involved in the pathological blood pressure rise in the particular developmental period. On the other hand, our presented results compare the antihypertensive effects of the selected drugs only at the end of their administration in two stages of the early ontogenesis in SHR. Although we have shown that in this way it is possible to slow-down the development of hypertension in young SHR, some further studies are necessary to investigate whether the described therapeutic effects persist also after the finishing of the drug administration, and particularly to assess the resultant effect of the respective treatment on the adult cardiovascular phenotype. For example, the permanent decrease of blood pressure in SHR or in Prague hypertensive rats has never been observed after the brief therapeutic intervention using calcium channel blockers [35, 36]. In contrast, preventive treatment of young SHR with drugs affecting the renin-angiotensin system (inhibitors of angiotensin-converting enzyme; antagonists of AT_1 receptors for angiotensin II) may have prolonged or permanent effects on their cardiovascular function [37-39]. When the same kind of therapy was applied to animals older than 20 weeks, despite the apparent reduction of blood pressure during the active therapy, this effect was not observed after its interruption [39, 40].

Conclusion and future prospects

The aforementioned results can be considered as the evidence that during critical developmental periods the proper pharmacological treatment of rats, genetically predisposed to hypertension development, may have long-lasting beneficial effect on their cardiovascular phenotype. The described findings are mostly from the area of the basic research and do not provide the immediate realisation outputs in the clinical praxis, but they may significantly influence the evolution of new therapeutic strategies also in human subjects which are at high risk of future hypertension. It is obvious that in human medicine, the non-pharmacological attempt (mainly in terms of lifestyle changes) is preferred to prevent cardiovascular disease and mortality in patients whose blood pressure values are getting close to the lower limit of the hypertensive range. More studies are needed to assess the effects of different pharmacological drugs in prevention and treatment of human hypertensive state, also in connection with the safety and cost-effectivness of such interventions, and to determine whether particular drug classes are more effective than the others. At the same time, further experiments with animal models of hypertension could also be made in order to contribute to the basic biological knowledge about the function of the living systems and the possibilities of targeted modification of their properties during the early development.

Acknowledgement

The study was supported by grants VEGA No. 2/0193/11 and 2/0188/12.

REFERENCES

[1] H.F. Nijhout, *Evo. Dev*., **2003**, 5, 9-18.
[2] H.S. Callahan, M. Pigliucci, C.D. Schlichting, *BioEssays*, **1997**, 19, 519-525.
[3] M. Pigliucci, *Curr. Opin. Plant. Biol.*, **1998**, 1, 87-91.
[4] B. Weinhold, *Environ. Health Perspect.*, **2006**, 114, A161-A167.
[5] W. Reik, *Nature*, **2007**, 447, 425-432.
[6] A.P. Feinberg, *Nature*, **2007**, 447, 433-440.
[7] E.M. Meyerowitz, *Science*, **2002**, 295, 1482-1485.
[8] A. Fehér, T.P. Pasternak, D. Dudits, *Plant Cell Tissue Organ Cult.*, **2003**, 74, 201-228.
[9] A. Novoplansky, *Evol. Ecol.*, **2002**, 16, 177-188.
[10] B. Tzschentke, A. Plagemann, *World´s Poult. Sci. J.*, **2006**, 62, 626-638.
[11] S.F. Gilbert, *Dev. Biol.*, **2001**, 233, 1-12.
[12] P.D. Gluckman, M.A. Hanson, *Pediatr. Res.*, **2004**, 56, 311-317.
[13] J. Schwartz, J.L. Morrison, *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2005**, 288, R11-R15.
[14] B.T. Alexander, *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **2006**, 290, R1-R10.
[15] J.R. Challis, D. Sloboda, S.G. Matthews, A. Holloway, N. Alfaidy, F.A. Patel, W. Whittle, M. Fraser, T.J.M. Moss, J. Newnham, *Mol. Cell. Endocrinol.*, **2001**, 185, 135-144.
[16] F.H. Bloomfield, M.H. Oliver, P. Hawkins, M. Campbell, D.J. Phillips, P.D. Gluckman, J.R.G. Challis, J.E. Harding, *Science*, **2003**, 300, 606.
[17] M. McLean, R. Smith, *Reproduction*, **2001**, 121, 493-501.
[18] E.W. Hillhouse, D.K. Grammatopoulos, *Reproduction*, **2002**, 124, 323-329.
[19] C. Amiel-Tison, D. Cabrol, R.J. Denver, P.H. Jarreau, E. Papiernik, P.V. Piazza, *Early Hum. Dev.*, **2004**, 78, 15-27.
[20] D.J. Barker, P.M. Clark, *Rev. Reprod.*, **1997**, 2, 105-112.
[21] S.G. Matthews, *Trends Endocrinol. Metab.*, **2002**, 13, 373-380.
[22] B.H. Breier, M.H. Vickers, B.A. Ikenasio, K.Y. Chan, W.P.S. Wong, *Mol. Cell. Endocrinol.*, **2001**, 185, 73-79.
[23] P.D. Gluckman, M.A. Hanson, A.S. Beedle, *Am. J. Human Biol.*, **2007**, 19, 1-19.
[24] J.V. Neel, A.B. Weder, S. Julius, *Perspect. Biol. Med.*, **1999**, 42, 44-74.
[25] C.N. Hales, D.J. Barker, *Br. Med. Bull.*, **2001**, 60, 5-20.
[26] J. Kuneš, J. Zicha, *Physiol. Res.*, **2009**, 58, S33-S41.
[27] E.D. Frohlich, *J. Hypertens.*, **1986**, 4, S15-S19.
[28] J. Zicha, J. Kuneš, *Physiol. Rev.*, **1999**, 79, 1227-1282.
[29] J.G. Dickhout, R.M.K.W. Lee, *Am. J. Physiol. Heart Circ. Physiol.*, **1998**, 274, H794-H800.
[30] O. Pecháňová, J. Zicha, L. Paulis, W. Zenebe, Z. Dobešová, S. Kojšová, L. Jendeková, M. Sládková, I. Dovinová, F. Šimko, J. Kuneš, *Eur. J. Pharmacol.*, **2007**, 561, 129-136.
[31] S.F. Pang, F. Tang, P.L. Tang, *J. Exp. Zool.*, **1984**, 229, 41-47.
[32] M. Tabačeková, J. Török, A. Zemančíková, J. Parohová, S. Vranková, *Kidney Blood Press. Res.*, **2001**, 35, 201.
[33] A. Zemančíková, J. Török, *Physiol. Res.*, **2009**, 58, 921-925.
[34] J. Kuneš, Z. Dobešová, J. Zicha, *Physiol. Res.*, **2003**, 52, 50P.
[35] D. Rizzoni, M. Castellano, E. Porteri, G. Bettoni, M.L. Muiesan, E. Agabiti Rosei, *Hypertension*, **1994**, 24, 131-139.
[36] J. Heller, S. Hellerová, *Kidney Blood Press. Res.*, **1998**, 21, 445-451.
[37] S.B. Harrap, W.M. Van der Merwe, S.A. Griffin, F. MacPherson, A.F. Lever, *Hypertension*, **1990**, 16, 603-614.
[38] J.J. Morton, E.C. Beattie, F. MacPherson, *J. Vasc. Res.*, **1992**, 29, 264-269.
[39] J. Zicha, Z. Dobešová, S. Hojná, J. Kuneš, *Hypertension*, **2005**, 46, 912.
[40] C.K. Kost jr, P. Li, E.K. Jackson, *Hypertension*, **1995**, 25, 82-87.