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REVIEW

Critical Developmental Periods in the Pathogenesis of Hypertension

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Summary

Hypertension is one of the major risk factor of cardiovascular diseases, but after a century of clinical and basic research, the discrete etiology of this disease is still not fully understood. One reason is that blood pressure is a quantitative trait with multifactorial determination. Numerous genes, environmental factors as well as epigenetic factors should be considered. There is no doubt that although the full manifestation of hypertension and other cardiovascular diseases usually occurs predominantly in adulthood and/or senescence, the roots can be traced back to early ontogeny. The detailed knowledge of the ontogenetic changes occurring in the cardiovascular system of experimental animals during particular critical periods (developmental windows) could help to solve this problem in humans and might facilitate the age-specific prevention of human hypertension. We thus believe that this approach might contribute to the reduction of cardiovascular morbidity among susceptible individuals in the future.

Key words

Critical developmental periods • Developmental programming • Hypertension • Epigenetics • Rat

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Introduction

Hypertension has many causes, but after a century of clinical and basic research, the discrete etiology of this disease is still not fully understood. The problem is that blood pressure is a typical quantitative trait with multifactorial determination. The interactions of multiple genetic and environmental factors as well as gene-gene interactions play a role causing the modification of various systems that adjust blood pressure (BP) to actual living conditions. One can say that hypertension develops as a consequence of errors in well-coordinated regulatory systems of BP. These errors in a cascade of genetic, biochemical and metabolic processes, which need not be robust, have enough potential to result in hypertension. Numerous observations indicate that although the full manifestation of hypertension and other cardiovascular diseases usually occurs in adulthood and/or senescence, the roots can be traced back to early ontogeny (Zicha and Kuneš 1999). The understanding of early changes preceding clinical manifestations of hypertension is essential for improving of preventive interventions.

This short review summarizes contemporary information on critical developmental periods (developmental windows), which could play an important role in the pathogenesis of experimental and human hypertension. Several times we have mentioned the importance of age in the pathogenesis of experimental hypertension (Zicha and Kuneš 1986, 1999, Kuneš and Zicha 2006). Moreover, the hypothesis of the fetal origins of adult diseases in humans was put forward by David Barker (Barker and Osmond 1988), who suggested that environmental factors, mainly nutrition, can lead to permanent metabolic and structural changes in the fetus and thus increasing the risk of many diseases in adulthood. The knowledge of molecular mechanisms, by which early minor environmental stimuli modify the expression of genetic information, might be the desired key for the understanding of mechanisms leading to the change of phenotype in adulthood (Kuneš and Zicha

2006). This gene-environmental interaction could be partially explained by epigenetic inheritance about which some information will also be presented.

"Critical developmental period": basic characteristic

The concept of "critical developmental period" was established more than fifty years ago as a general theory applied to organization processes involved in the development of any living system (Scott *et al.* 1974). One should keep in mind that the development of such system corresponds with the propagation of genetic information in particular environment. Therefore, the critical developmental period means the existence of stages, in which the development is more sensitive to specific environmental factors. Moreover, during the whole individual development one can recognize relatively stable periods while other periods with higher sensitivity to particular changes. There are also very important findings that developmental changes cannot be detected immediately after the intervention. On the contrary, a certain delay is always present, so that, one can speak about the "late consequences of early alterations". There is no doubt that the critical developmental periods are much better recognized and characterized in experimental animals than in humans (Křeček 1971, Zicha and Kuneš 1999). However, basic ontogenetic principles governing hypertension development in rat and human are often surprisingly similar. A typical example is a fetal period, in which programming of adult BP occurs in both in humans and in spontaneously hypertensive rats (Barker and Osmond 1988, Zicha and Kuneš 1999). The existence of the cascade of critical developmental periods (developmental windows), through which each organism (i.e. rat and human being) must pass during ontogeny, helps to explain the considerable variability of the cardiovascular phenotype in adulthood.

However, for readers, there is some perplexity of scientific literature due to the different nomenclature of these developmental processes. One can find the term developmental window, fetal programming, developmental origins, ontogenetic aspects, etc. usually expressing a little bit different point of view. Some of them are focused only on a short period of development, e.g. fetal programming, while the others try to cover the whole life. If we speak about the distinct developmental periods, which are critical for changes leading to disease development, we should use the term critical developmental period or developmental window.

Surprisingly, developmental physiology has paid only little attention to the problem of critical developmental periods. If we look at the developing organism from the point of view of its relationship to the environment, it is clear that the developing organism represents an "ideal terrain" for induction of many modifications, which could have short- or long-lasting effects. There is a very important period for the developing organism, in which it is more or less dependent on the mother. This includes the interval between the fertilization of the egg and weaning. This period is relatively very short. It represents about 6 % in the rat and even less in man – about 2 % of the total life span. There is no doubt that the altered fetal nutrition (independent of the reason), might affect fetal development. Since a part of the induced changes is mediated by enhanced access of glucocorticoids to the fetus, it is not surprising that different tissues and organs, including cardiovascular ones, are affected. Lower birth weight is, therefore, accompanied by abnormalities predisposing the organism to increased incidence of cardiovascular and/or metabolic diseases (Hoet and Hanson 1999). It should be kept in mind that even minor changes in fetal nutrition can modify metabolic programming of the organism and alter its susceptibility to other environmental factors acting in later stages of ontogeny (Ozanne 2001). Of course, it is true, that the interactions of each organism with the environmental factors continue during the whole life, so that other developmental periods could also be critical for the disease development.

Critical developmental periods in experimental hypertension

Rat is an ideal model for studying developmental aspects of hypertension and other diseases. The main advantage of this species seems to be the availability of numerous strains with different predispositions to the occurrence of hypertension. Moreover, one can study practically all their developmental stages in a very short period of time. Distinct postnatal age periods can be specified in rats according to the essential changes in the mother-pups interactions, nutrition and digestion, water and electrolyte metabolism, gonadal activity, etc. (Křeček 1971, Zicha and Kuneš 1986, 1999). Therefore, the life of rat could be divided into several distinct periods, e.g. intrauterine, perinatal, suckling, weaning, prepuberty, the

period of sexual maturation and adulthood. This periodization is very important for the interpretation of available data since some environmental interactions have different effects if applied in different age periods.

The intrauterine period varies from 21 to 23 days and is terminated by birth when the fetal circulation, oxygen supply, nutrition and other physiological functions are profoundly rearranged. The birth starts perinatal and suckling periods when pups drink milk as the only source of water and nutrients during the first 14 days of the life. At the end of the second postnatal week, pups open their eyes, change their thermoregulation and begin to move actively. During this period the pups start to change their nutritional pattern, i.e. start to consume solid food and drink water parallelly to milk. This weaning period is terminated at the age of 28 days when pups start to be completely independent of their mother. It should be noted that some controversial results obtained in animals from various colonies could result from the different duration of mother-pups interaction in this developmental periods. Some breeders wean rat pups prematurely, i.e. at the age of 19-23 days, and thus their phenotypes could be different in comparison with those weaned regularly at the age of 28 days. After the weaning period the rats proceed through about 2 weeks until puberty, which begins around the age of 45 days and is terminated in animals aged 60-70 days. The qualitative changes in the structure and function of particular systems seen during maturation are followed by quantitative changes occurring in adulthood. In contrast to the relatively precise definition of the above developmental periods, the onset of senescence in the rat is not quite clear. Usually rats older than 24 month are regarded as aged, however, there are differences in the longevity between various rat strains (Folkow and Svanborg 1993). Each developmental period is associated with a dynamic sequence of events leading to the expression of genomic information responsible for the characteristic transformation of particular regions of the cardiovascular system (Zicha and Kuneš 1999).

Critical periods for blood pressure development in the rat could be preferentially indicated by the research of salt-dependent forms of experimental hypertension. Young rats are more susceptible to various salt-dependent forms of hypertension than the adult ones and the magnitude of the hypertensive response to high salt intake progressively diminishes with age from which this stimulus begins to influence of the organism (Brownie *et al.* 1966, Dlouhá *et al.* 1979, Zicha and Kuneš 1986). There is no doubt that weaning and prepubertal periods are critical for the development of various forms of experimental salt hypertension (Zicha and Kuneš 1986). It is evident that BP response to high salt intake might involve only those mechanisms that are available in the given stage of development, in which the stimulus is applied. In other words, the activation of distinct pathogenetic mechanisms in young and adult animals exposed to such environmental stimuli could elicit completely different long-term cardiovascular effects (Křeček *et al.* 1982, Zicha and Kuneš 1986). The importance of the critical periods for the therapy of salt hypertension was also demonstrated (Zicha *et al.* 1984, 1987, Zicha and Kuneš 1986). Several authors have demonstrated that antihypertensive therapy is more efficient when started during weaning period and it could have even preventive character. When the same therapy was started in adulthood, the effect was minimal or none. This age-dependent therapeutical effect was also demonstrated in spontaneously hypertensive rats (Harrap *et al.* 1990, Zicha and Kuneš 1999, Zicha *et al.* 2008).

The detailed knowledge of the ontogenetic changes occurring in the cardiovascular system of experimental animals during particular critical periods (developmental windows) could help to solve this problem in humans and might facilitate the age-specific prevention of human hypertension.

Critical developmental periods and human hypertension

During the second half of the last century several papers were published showing the relation between early life events and later cardiovascular diseases in humans (Rose 1964, Forsdahl 1977). One can say that this relation is one of the most exciting phenomena in epidemiology. Rose (1964) reported the association of ischemic heart disease and infant mortality within the same families and Forsdall (1977) showed that the incidence of atherosclerotic heart disease could be correlated with infant mortality rate of the same population. In 1986, David Barker and colleagues were searching for an explanation of the different rates of mortality from stroke and cardiovascular diseases in a well documented population in England and Wales (Barker and Osmond 1986). They postulated that the geographical distribution of mortality rates from stroke and cardiovascular diseases in 1968-1978 was closely related to the neonatal mortality in 1921-1925 suggesting

that poor health and physique of mothers were the important determinants of the risk of stroke in their babies.

Later on, Barker *et al.* (1990) reported that BP in adulthood was related not only to the birth weight but inversely related also to the placental weight. This study led to the hypothesis that the intrauterine growth restriction, through an inappropriate function of placenta, causes circulatory adaptation and altered arterial structure in the fetus leading to hypertension in adulthood as well as to the higher incidence of cardiovascular morbidity (Fig. 1). The "early or fetal origin" hypothesis was formulated. This hypothesis suggests that the insults at critical periods during the fetal development can lead to permanent metabolic and structural changes in the fetus increasing its risk of many diseases in the adulthood (Barker and Osmond 1988). Barker expected that fetus growth restriction is due to intrauterine malnutrition. Numerous studies suggested different explanations for the association between the intrauterine growth restriction and adult BP. Brenner *et al.* (1988) proposed that one of the possibilities could be a smaller nephron number in patients with low birth weight, leading to glomerular hyperfiltration and hypertension in adulthood. This was proven in postmortem study (Keller *et al.* 2003). However, this phenomenon is rather complex because genetic factors could also play a significant role. Recently, a new hypothesis proposed that genetically determined insulin resistance could cause the impaired insulin-mediated growth of the fetus and insulin resistance in adulthood. Thus, adult phenotypes – insulin resistance, diabetes and hypertension – could be a consequence of an insulin-resistant genotype, which manifests itself already *in utero*. This insulin hypothesis is supported by recent results of Schlemm *et al.* (2010) showing that fetal angiotensinogen M235T polymorphism is associated with the low birth weight and elevated fetal total glycated hemoglobin.

From the point of view of critical developmental periods, it is evident that the intrauterine period is a major critical period for human essential hypertension. The changes of intrauterine environment, including placenta size, are manifested in birth weight and this is somehow related to BP in adulthood. This was summarized in several recent reviews (Law and Shiell 1996, Huxlay *et al.* 2002) indicating a negative relationship between blood pressure and the birth weight. However, the intrauterine period is not the only critical period for human hypertension. We believe that detailed knowledge about critical developmental periods in rats, mainly in those with genetic or salt hypertension, will help to recognize other developmental periods responsible for hypertension development in humans. At least, they could indicate the relative importance of the particular ontogenetic stages for BP effects of pharmacological or nutritional interventions, which might be completely ineffective if applied at an inappropriate age.

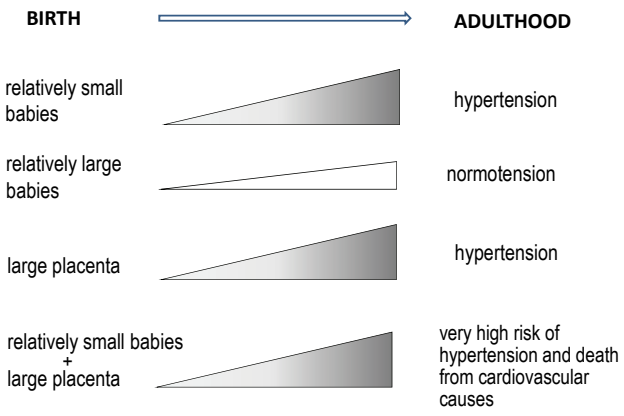

Fig. 1. Birth weight and placental size as a determinant of blood pressure in adulthood.

Late cardiovascular effects of interventions in critical developmental periods

It is evident from the above information that most of the proofs for late cardiovascular effects of interventions in the critical developmental periods came from studies in experimental animals. An effective study of particular cardiovascular alterations emerging in the course of developmental process, from their early onset until their late consequences, requires particular time and adequate models. These models should be genetically well-defined, accessible for techniques used in cardiovascular physiology and economically acceptable. Moreover, their life span must be short enough as compared to that of the investigator (Zicha and Kuneš 1999). Therefore, especially rats are very useful for such studies, although mice started to be also often used because they are more appropriate tool for genetic manipulations (Cvetkovic and Sigmund 2000).

Detailed information about the age-dependent influence of particular systems, which could modify the development of the cardiovascular apparatus, may lead to a more effective hypertension treatment and also to its better prevention. One of the most important systems

influencing the development of cardiovascular apparatus is the renin-angiotensin system (RAS). This system has long been recognized as a principle regulator of arterial blood pressure and is thought to play a pivotal role in the pathogenesis of human and experimental hypertension (Inagami 1994, Iwanami *et al.* 2009). Chronic treatment with angiotensin converting enzyme (ACE) inhibitors lowers BP and normalizes the altered structure of resistance vessels in patients with established essential hypertension (Schiffrin *et al.* 1994, Ruiz-Ortega *et al.* 2001, Julius *et al.* 2006). However, several studies have demonstrated that the magnitude of blood pressure lowering effects of ACE inhibitors did not correlate with their action on ACE in plasma and lung endothelium as well as on generation of angiotensin II in plasma (Johnston *et al.* 1988, Campbell 1996) suggesting that the tissue more than peripheral RAS are involved in hypertension development (Peers *et al.* 2001). A highly unique aspect of ACE inhibitors or angiotensin receptor type 1 (AT_1) blockers as antihypertensive drugs is that short-term treatment of young spontaneously hypertensive rats (SHR) with these compounds fully prevented the development of hypertension later in life (Giudicelli *et al.* 1980, Harrap *et al.* 1990, Wu and Berecek 1993). It has been demonstrated that the effect of antihypertensive therapy with ACE inhibitors is really age-dependent (Fig. 2). As can be seen, the therapy in adult animals had only transient effects. The same was true when young and adult SHR were treated with ACE inhibitor captopril. The treatment from the weaning period resulted in the prevention of hypertension development and this antihypertensive effect was seen even 12 weeks after stopping the therapy. In the adult animals, the effect on established hypertension was minimal and there was no effect after the withdrawal of the treatment. This supports the idea that the plasticity of immature organism contrasts with "rigidity" of mature organism (Zicha *et al.* 2010).

The critical periods could be seen even in gene therapy with so-cold late effects of early intervention. Recently, it was demonstrated that a single perinatal injection of angiotensin AT_1 receptor antisence cDNA gene to immature SHR (aged 5 days) caused a long-term attenuation of hypertension development (Lu *et al.* 1997). This attenuation lasted up to 7 month of age. The same procedure performed in adult animals had only a transient character and lasted up to one month (Katovich *et al.* 1999). It is of interest that such an early gene therapy lowered BP just at the age of 4-12 weeks, i.e. in the critical period (developmental window), in which transient antihypertensive therapy is capable to induce long-term BP reduction persisting even after drug withdrawal (Zicha and Kuneš 1999). Moreover, Chao and colleagues have reversed systemic hypertension in adult rats by overexpressing several vasodilator genes and this lowering of BP was transient lasting only few weeks (Chao and Chao 1997, Lin *et al.* 1997, Chao *et al.* 1999). It is interesting that this procedure was successful in different rat models of hypertension (SHR, Dahl salt-sensitive, renal hypertensive, etc.). This suggests that some mechanisms could be common for hypertension development, so that, the results from experimental studies might be transferred to human essential hypertension.

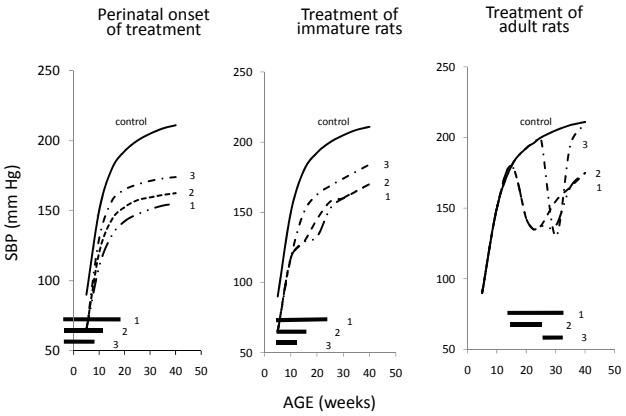

Fig. 2. The age-dependent effects of chronic ACE inhibitor treatment and its withdrawal on hypertension development in SHR.

Epigenetic inheritance and hypertension development

The term "epigenetics" has different meanings to different people and has evolved over the time. It was introduced by Conrad Wadington in 1942 whose "epigenetic landscape" is a metaphor for how gene regulation modulates the development (Goldberg *et al.* 2007). He demonstrated how mutation could affect this landscape and used this metaphor in his discussions on the evolution – he was the first person to emphasize that the evolution occurred mainly through mutations that affected developmental anatomy. Holliday defined epigenetics as "the study of the mechanisms of temporal and spatial control of gene activity during the development of complex organisms". Thus, epigenetics can be used to describe anything else than DNA sequence

that influences the development of an organism. The modern usage of this word in scientific milieu is narrower, referring to the heritable traits that do not involve changes of the underlying DNA sequence. The Greek prefix epi- in epigenetics implies features that are "on top of" or "in addition to" genetics; thus epigenetic traits exist in addition to the traditional molecular basis for inheritance.

Epigenetic mechanisms are affected by several factors and processes including the development *in utero* and in childhood, environmental chemicals, drugs and pharmaceuticals, aging, and diet. The molecular basis of epigenetics is complex but it does not involve the modification of the basic structure of DNA. Additionally, the chromatin proteins associated with DNA may be activated or silenced. This accounts for why the differentiated cells in a multicellular organism express only those genes that are necessary for their own activity. Epigenetic changes are preserved when cells divide. Most epigenetic changes occur only within the course of one individual organism's lifetime, but if such a change has been caused in a sperm or an egg cell utilized in fertilization, then some epigenetic changes are inherited from one generation to the next (Chandler 2007). Epigenetic research uses a wide range of molecular biology techniques for better understanding of epigenetic phenomena. So that, it is clear that at least some epigenetic modifications are heritable, passing from parents to offspring, although they are not inherited by the same mechanism as a typical genetic information, which is encoded in the sequences of nucleotides that make up the DNA. This information is therefore passed from generation to generation faithfully because the DNA replication process is accurate. Epigenetic information, however, is inherited only if these modifications are again generated on newly synthesized DNA or proteins. Some forms of epigenetic modification are faithfully transmitted, but others may be "erased" or "reset", depending on a variety of factors.

The principal type of epigenetic modification is DNA methylation, which occurs when methyl groups, an epigenetic factor found in some dietary sources, can tag DNA and activate or repress some genes (Fig. 3). Methylation can be transient and can change rapidly during the life span of a cell or an organism, but it can be completely permanent if it is set early in the development of the embryo. Another largely permanent chemical modification is histone acetylation occuring when the binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated. All of these factors and processes can have an effect on human health, possibly resulting in cancer, autoimmune diseases, mental disorders, cardiovascular diseases or other illnesses.

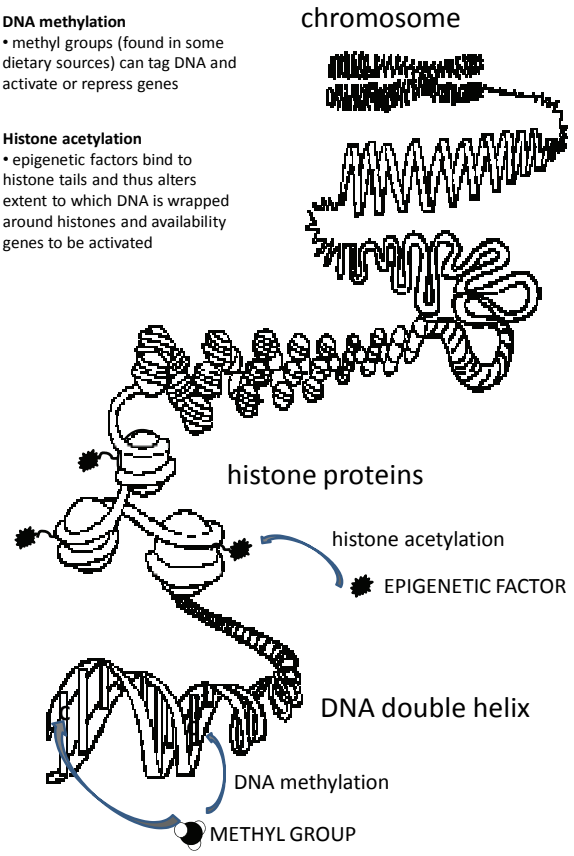

Fig. 3. Epigenetic mechanisms.

There is no doubt that gene-environmental interaction play a significant role in the etiology of hypertension. One would expect that the environmental impact on genetic information is exerted *via* DNA damage, but epigenetic inheritance seems to be more responsible (Kuneš and Zicha 2006). Several recent studies demonstrated how environmental factors can modify epigenetic processes, thereby affecting epigenetic marks and downstream patterns of gene expression in specific cells and cell lineages (Gluckman *et al.* 2007, Ho and Tang 2007, Waterland and Michels 2007, Feinberg 2008). In pregnant rats, protein restriction during gestation reduces methylation of the promoter region of the gene that codes for glucocorticoid receptor in offspring liver cells (Lillycrop *et al.* 2007, Erhuma *et al.* 2009). This leads to the amplification of the liver`s

metabolite response to stress hormones. Moreover, it was demonstrated that pups of mothers on low protein diet overexpres of the AT_{1b} receptor mRNA and protein in the adrenal gland suggesting its contribution to the elevated blood pressure seen in these animals (Bogdarina *et al.* 2007). The expression of AT_{1a} receptor was normal. However, such results could not be simply transferred into human pathology because human genome contains a single AT_1 receptor gene, which is widely expressed in a pattern similar to that of AT_{1a} receptor in rodents (Inagami 1995). Our understanding of the contribution of epigenetics to hypertension and other cardiovascular diseases should be increased as mentioned in several recent reviews (Turunen *et al.* 2009, Ordovas and Smith 2010).

Perspectives and concluding remarks

It is evident that the search for the causes of essential hypertension is not easy due to its multifactorial character. Although there are some data about the potential candidate genes and environmental risk factors, enormous difficulties are still faced in tracing the development of this disease back to its origin. Fetal programming is the most striking example of how important is the developmental approach for the study of chronic multifactorial diseases based on gene-environmental interactions. In this review we presented a very short insight into this topic. We have tried to specify some critical periods (developmental windows) for experimental and human hypertension. The existence of the cascade of critical developmental periods, through which each organism must pass during ontogeny, helps to explain the variability of cardiovascular phenotypes in adult organisms.

Physicians are interested in knowing whether disease can be prevented by reducing exposure to environmental risks. Gene-environment interaction means that some people carry genetic factors that confer susceptibility or resistance to a certain disorder in a particular environment. It has been argued that there may be significant public health benefits in using genetic information to stratify the allocation of environmental interventions that prevent disease, although this viewpoint is not universally accepted. Moreover, the better understanding of epigenetic mechanisms may support our decisions to reduce the influence of the environmental factors and thus to decrease the risk of hypertension. However, whereas the genomic information is the same in all cells of the organism and during the whole lifespan, the epigenetic information varies from cell to cell and during the ontogeny. It is evident from many experimental data that the restriction of major risk environmental factors could be effective in the prevention of hypertension mainly if it is applied in the precise critical periods. There is no doubt that at least pregnant women with familial history of hypertension should be encouraged to check their diet and lifestyle and be convinced of prevention measures directed to the progeny. We believe that this might contribute to the reduction of cardiovascular morbidity among susceptible individuals.

Conflict of Interest

There is no conflict of interest.

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