REVIEW

Research on Experimental Hypertension in Prague (1966-2009)

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Summary
The study of ontogenetic aspects of water and electrolyte metabolism performed in the Institute of Physiology (Czechoslovak Academy of Sciences) led to the research on the increased susceptibility of immature rats to salt-dependent forms of hypertension since 1966. Hemodynamic studies in developing rats paved the way to the evaluation of hemodynamic mechanisms during the development of genetic hypertension in SHR. A particular attention was focused on altered renal function and kidney damage in both salt and genetic hypertension with a special respect to renin-angiotensin system. Renal damage associated with hypertension progression was in the center of interest of several research groups in Prague. The alterations in ion transport, cell calcium handling and membrane structure as well as their relationship to abnormal lipid metabolism were studied in a close cooperation with laboratories in Munich, Glasgow, Montreal and Paris. The role of NO and oxidative stress in various forms of hypertension was a subject of a joint research with our Slovak colleagues focused mainly on NO-deficient hypertension elicited by chronic L-NAME administration. Finally, we adopted a method enabling us to evaluate the balance of vasoconstrictor and vasodilator mechanisms in BP maintenance. Using this method we demonstrated sympathetic hyperactivity and relative NO deficiency in rats with either salt-dependent or genetic hypertension. At the end of the first decennium of this century we were ready to modify our traditional approach towards modern trends in the research of experimental hypertension.

Keywords: Salt-dependent hypertension • Genetic hypertension • Body fluids • Hemodynamics • Ion transport • Cell membrane structure and function • Renal function • Renin-angiotensin systems

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Our teachers

Physiological changes occurring during the ontogenesis belong to the historical research topics in the Institute of Physiology (Czechoslovak Academy of Sciences) (IPHYS). Water and electrolyte metabolism, body fluid distribution, renal function and vasopressin action were studied in developing rats since 1954 [1,2]. Dr. Jiří Jelínek focused his attention to the characteristic changes of water, sodium, potassium and chloride content in the body and body fluids of laboratory rats in particular developmental periods (suckling, weaning, prepuberty) [3,4]. Later he was inspired by the paper of Guillebeau and Skelton [5] who reported that immature rats are more susceptible to the induction of salt hypertension elicited by adrenal regeneration after its enucleation. In 1966 he published two papers indicating that not only adrenal-regeneration hypertension but also deoxycorticosterone (DOCA)-salt hypertension are more severe and self-sustaining in young than in adult animals [6-8]. Jelínek´s research group paid a special attention to the study of changes in body fluids, renal function and structure with a special attention to renin-angiotensin system (RAS) [9-15]. They also performed fundamental studies on salt hypertension in monkeys (*Papio hamadrys*), indicating a greater blood pressure elevation (BP) in primates exposed to high salt intake from birth as compared to those exposed to this hypertensinogenic factor during sexual maturation. On the other hand, in adult salt hypertensive primates there was enhanced pulse pressure and reduced plasma volume as compared to control animals. They also demonstrated that blood pressure was inversely related to plasma volume in salt hypertensive monkeys [16,17].

In parallel, Prof. Jiří Křeček, who investigated the antidiuretic action of vasopressin in suckling and weanling rats [2,18,19], also started to study developmental aspects of salt hypertension using a peculiar model of uninephrectomized vasopressin-deficient Brattleboro rats drinking 0.6 % saline [20]. His experiments indicated that the age-dependent salt hypertension can be elicited even in the absence of vasopressin [21] and that prepuberty seems to be a critical period for the induction of more pronounced form of salt hypertension [22]. Subsequent hemodynamic studies, which used a dye dilution technique for the estimation of cardiac output in conscious animals [23], confirmed a significant BP elevation due to the increase in peripheral resistance and a major reduction of arterial compliance in young but not in adult animals with the above form of salt hypertension [24].

Newly formed research group

In 1983 two young investigators from the above research groups – Dr. Jaroslav Kuneš and Dr. Josef Zicha – formed an independent research team and combined their methodical experience on body fluids and hemodynamic measurements in order to study further aspects of age-dependent salt hypertension. Using homozygous and heterozygous Brattleboro rats we demonstrated that sodium retention, which is not accompanied by sufficient water retention, did not induce of DOCA-salt hypertension. Thus, antidiuretic rather than vasopressor effects of vasopressin are important for the development of DOCA-salt hypertension [25-27]. Another important topic of our study was the age-dependent role of digoxin-like factor (DLF) in BP maintenance in young and adult rats with DOCA-salt hypertension. Using the approach of Kojima *et al.* [28] based upon the acute administration of antidigoxin antibody, we found that endogenous DLF is important for BP maintenance especially in young DOCA-salt hypertensive rats [29,30], while this was not true for adult BP-matched rats with either DOCA-salt or spontaneous hypertension [31]. These findings were esteemed by Demuth Prize (Young Investigator Award of International Society of Hypertension, Interlaken 1984). Our subsequent review in *Hypertension* [32] suggested that prepuberty might be a critical period for enhanced salt-induced DLF production (Fig. 1). The third interesting field of our research was the role of sodium and chloride in the development of DOCA-salt hypertension. At that time there was an idea that chloride might be more important than sodium in the pathogenesis of salt-dependent forms of hypertension [32-36]. Our hemodynamic studies [37-39] revealed the delayed induction of hypertension and the absence of decreased arterial compliance in DOCA-treated rats, in which the dietary NaCl was replaced by $NaHCO_3$ to avoid the excess chloride intake.

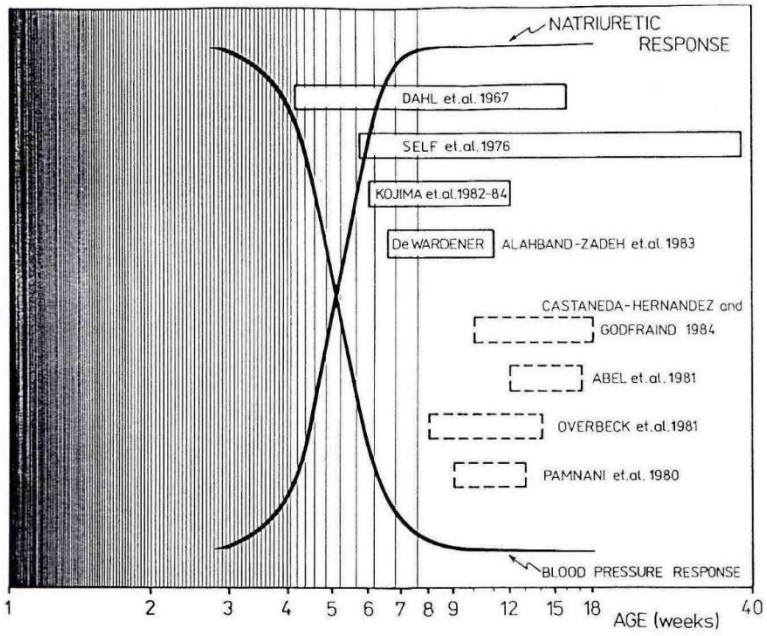

Fig. 1. The inverse relationship of natriuretic response to plasma volume expansion [176] and blood pressure response to high salt intake during prepuberty and puberty [21,177]. Full horizontal bars indicate the onset and duration of high salt intake in the studies revealing a positive evidence for digoxin-like natriuretic factor [178-181], whereas negative studies are depicted as broken bars [182-185]. The density of vertical lines reflects the intensity of maturation processes. Modified from our review [32].

The research of genetic hypertension at the IPHYS in Prague was started by Dr. Ivan Albrecht who received first breeding pairs of spontaneously hypertensive rats (SHR) from Prof. Yukio Yamori in 1972. His measurements of cardiac output revealed that the prepuberty is a hyperkinetic phase of hypertension development in SHR [40,41]. Furthermore, on the basis of his original pharmacological interventions he proposed the prepuberty as a critical period for the development of genetic hypertension in this rat strain [42]. In 1981 Dr. Kuneš joined the laboratory of Dr. Pavel Hamet in Montreal and they started a long-term cooperation on the research of several important aspects of genetic hypertension. At the beginning they were interested in cardiac and renal hyperplasia of newborn SHR [43-46]. Ontogenetic aspects of hypertension development in the rat were later reviewed in *Physiological Reviews* in 1999 [47].

Jiří Heller and Prague hypertensive rats

In the late 80ties Dr. Jiří Heller (Institute of Clinical and Experimental Medicine, Prague) developed a new model of genetic hypertension based upon Wistar rats – Prague hypertensive (PHR) and normotensive (PNR) rats [48]. This form of hypertension had many features similar to SHR but the main advantage of this model was that PHR and PNR had no histocompatibility problems so that kidneys could be transplanted between both lines without any signs of rejection [49,50]. The cross-transplantation of PNR kidney to bilaterally nephrectomized PHR animal lowered its blood pressure, while the transplantation of PHR kidney to PNR always induced hypertension development. This was true even if the transplanted kidney originated from PHR animals treated with antihypertensive drugs (captopril or nifedipine) since weaning [49]. A later study [50] indicated that the transplanted PHR kidney is important for the development but not for the maintenance of this Prague form of genetic hypertension. Using isolated kidneys from this model, Vaněčková *et al.* [51] reported the impairment of renal sodium excretion in adult PHR animals. Renal endothelin system was considered to be a possible candidate for a "hypertensinogenic" substance produced by PHR kidney [52].

Blood pressure and proteinuria were lowered in both PHR and PNR by chronic administration of AT_1 receptor inhibitor losartan, which also prevented later development of renal damage in PHR animals [53]. One of the most fascinating findings in this rat strain was the demonstration of long-term blood pressure effects elicited by a brief treatment of young PHR with antihypertensive drugs inhibiting renin-angiotensin system. The beneficial BP effects were observed in 30-week-old PHR treated with losartan or perindopril at the age 5-9 weeks. Blood pressure reduction was even enhanced if this antihypertensive intervention was repeated at the age of 15-19 weeks. In addition, this long-term BP reduction was accompanied by a substantial antiproteinuric effect [54]. Blood pressure effects of early RAS blockade in PHR were considerably greater than those that we observed in similarly treated SHR [55].

Recombinant inbred strains as a research tool in the research of genetic hypertension

A major stimulus for further research of the genetics in SHR was the establishment of recombinant inbred (RI) strains derived from SHR and normotensive BN.lx rats by Prof. Vladimír Křen and Dr. Michal Pravenec [56,57]. Blood pressure in this set of RI strains was initially determined by Dr. Kuneš using a direct carotid puncture [56]. Later he verified it by radiotelemetry measurement [58].The initial papers started a very productive international cooperations (Theodore W. Kurtz, Tim J. Aitman, Pavel Hamet) leading to numerous highly cited papers [59-64] in prestigious journals including *Nature Genetics* [64-70]. A part of the results on the role of RI strains in the progress of genetics in SHR was summarized by Pravenec *et al.* [71,72]. However, the history of this extraordinary successful international research would deserve a separate review.

Red cell ion transport in experimental hypertension

At the same time Dr. Zicha received the breeding pairs of inbred salt-sensitive (SS/Jr) and salt-resistant (SR/Jr) Dahl rats [73] from Prof. John P. Rapp (Toledo, OH). In these rats we studied red cell ion transport, effect of dietary calcium on blood pressure, alterations in arterial baroreflex function, changes in particular compartments of body fluids, adrenergic vascular innervation etc. [74-78]. In 1987-1988 Dr. Zicha studied the kinetics of ouabain-sensitive Na^+ and K^+ transport in erythrocytes of young and old Dahl rats in the laboratory of Prof. Jochen Duhm in Munich. The data obtained in Munich [79] confirmed our earlier study done in Prague [74], which disclosed the

enhanced ouabain-sensitive ion transport in red blood cells but a reduced activity of Na^+-K^+-ATPase in young salt hypertensive SS/Jr rats. The explanation of these experimental findings was simple but shocking. Salt hypertension in Dahl rats was associated with two major kinetic abnormalities of Na^+-K^+ pump – the combination of increased affinity for internal sodium and decreased maximal transport rate. The former alteration is responsible for the enhanced ouabain-sensitive Na^+ and K^+ transport (studied under low physiological concentrations of internal sodium), while the latter kinetic change caused the decreased Na^+-K^+-ATPase activity (determined under saturating Na^+ concentrations) [74,79]. Our further studies on membrane ion transport in Dahl rats indicated that the altered function of Na^+-K^+ pump was related to abnormalities in cholesterol metabolism rather than to a mutation in *Atp1a1* gene [80-82].

In the early 90´s Dr. Hasan Karama Bin Talib from Yemen made his PhD Thesis in our lab. He was trained in the study of red cell ion transport at Prof. Alan R. Chipperfield (Dundee, UK). Thanks to his dedication to experimental work we were able to extend our ion transport studies to further hypertensive models such as DOCA-salt treated rats [83,84], hereditary hypertriglyceridemic rats [85] or SHR and RI strains [86]. Our papers indicated that enhanced inward sodium leak and/or augmented Na^+-K^+-cotransport are responsible for the increased red cell Na^+ content, which is compensated by the acceleration of ouabain-sensitive Na^+ extrusion by the Na^+-K^+ pump. This was in line with our cooperative study with Dr. Sergei N. Orlov [87] which revealed a higher Na^+-K^+-ATPase activity and enhanced passive K^+ permeability in erythrocytes of SHR compared to WKY or BN.lx rats. The findings on the red cell Na^+ and K^+ transport in experimental hypertension were later summarized in our reviews [88,89].

New cooperations, new possibilities, new challenges

After the Velvet revolution the close cooperation of Dr. Zicha and Dr. Kuneš continued not only in traditional but also in newly added fields. They became to be the Editors of the journal *Physiological Research* (formerly *Physiologia bohemoslovaca*) published by IPHYS since 1954. Dr. Kuneš returned from his second stay in Montreal where the attention was focused on numerous genetic determinants of high BP in SHR - HSP70 [90-92], HSP27 [93], stress genes [94], major histocompatibility complex [95] etc. In 1993 Dr. Kuneš accepted a surprising idea of Dr. Hamet to apply for the organization of the congress of the International Society of Hypertension in Prague 2002. Thus, we spent further 10 years not only with scientific research but also with the preparation of this major event which brought to Prague almost 8000 participants of the first Joint ISH/ESH Meeting (Fig. 2).

Fig. 2. Dr. Kuneš and Dr. Zicha with the President of ISH Prof. Kikuo Arakawa.

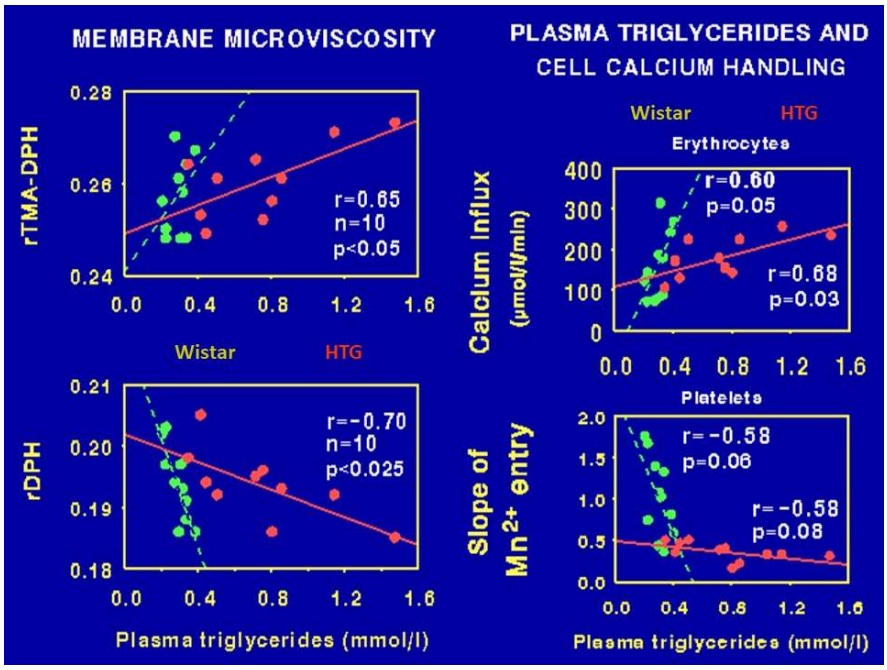

Fig. 3. The relationship of plasma triglycerides to membrane microviscosity (left panels) and cell calcium handling (right panels) in platelets of Wistar rats (green symbols) and HTG rats (red symbols). The data were published in our papers [110, 111].

A new model of Prague hereditary hypertriglyceridemic (HTG) rats was developed by Vrána and Kazdová [96] and a moderate hypertension was disclosed in these animals by our lab [97]. HTG rats were utilized to evaluate the relationship of abnormalities in BP, lipid and glucose metabolism or ion transport [85,97,98] with particular genetic determinants [99-101]. Further studies evaluated the role of *Cd36* and *Igf2* genes in this model of hypertension [102,103]. The findings obtained in HTG rats were summarized in two review papers [104,105].

In 1991 we established a long-term cooperation with Dr. Marie-Aude Devynck (Hospital Necker, Paris) on the analysis of alterations in membrane structure and function, cell calcium handling, intracellular pH regulation and platelet aggregation in several hypertensive models such as Sabra, Dahl, Lyon and HTG rats. Our first joint study, which was focused on the effects of sodium on membrane fluidity in platelets of Wistar rats, indicated that the changes of intracellular rather than extracellular sodium are responsible for the alterations of platelet membrane microviscosity in the membrane outer leaflet (TMA-DPH anisotropy) but not in the membrane lipid core (DPH anisotropy). Sodium depletion increased TMA-DPH anisotropy and sodium repletion lowered it [106]. The next study in Lyon hypertensive (LH) rats demonstrated a positive correlation of TMA-DPH anisotropy with the intracellular calcium (Ca^{2+}_i) in both platelets and erythrocytes, while DPH anisotropy correlated negatively with blood pressure and Ca^{2+}_i [107]. DPH anisotropy but not TMA-DPH anisotropy was reduced in erythrocytes of Sabra and Dahl rats prone to develop salt hypertension in which DPH anisotropy also correlated negatively with blood pressure [108]. Platelets of LH rats were characterized by substantially elevated basal Ca^{2+}_i values, higher Ca^{2+}_i levels after thrombin stimulation, and enhanced initial rate of thrombin-induced Mn^{2+} entry through the receptor-operated Ca^{2+} channels. Plasma triglycerides but not cholesterol seemed to be related to platelet calcium handling [109].

Platelet or erythrocyte Ca^{2+}_i values were similar in HTG and Wistar rats, the same was true for Ca^{2+} influx into erythrocytes. On the other hand, Ca^{2+}_i response to thrombin stimulation and Mn^{2+} entry through the receptor-operated Ca^{2+} channels were reduced in platelets of HTG rats [110]. Plasma triglycerides correlated positively with platelet TMA-DPH anisotropy and negatively with DPH anisotropy. These relationships were present in both HTG and Wistar rats but the slopes of these relationships were considerably smaller in HTG than in Wistar rats (Fig. 3). In addition, platelet Ca^{2+}_i correlated positively with TMA-DPH anisotropy and negatively with DPH anisotropy, but the slopes of these relationships were almost identical in both rat strains [111,112]. HTG rats were also characterized by platelet hypoaggregability. The initial rate of platelet aggregation was dependent on plasma triglycerides and the slope of this relationship was smaller

in HTG than in normotensive control rats [113]. Furthermore, we tried to increase circulating triglycerides by drinking of fructose solution or to lower them by gemfibrozil treatment. Chronic reduction of plasma triglycerides was associated with increased DPH anisotropy, while chronic increase of plasma triglycerides was accompanied by decreased DPH anisotropy [114].

Our experiments also revealed different platelet calcium handling in rats with salt-dependent hypertension (Sabra and Dahl rats) and those with genetic hypertension (Lyon rats). In the former rat strains there was a highly significant correlation of platelet Ca^{2+}_i with pulse pressure but not with diastolic blood pressure, whereas platelet Ca^{2+}_i in Lyon rats correlated with diastolic blood pressure but not with pulse pressure [115,116]. Finally, we also paid attention to the cytosolic pH (pH_i) and Ca^{2+}_i in platelets of Dahl and Sabra rats susceptible to salt hypertension development. Although there were no strain or salt-dependent differences in platelet Ca^{2+}_i, both strains had lower cytosolic pH_i [116,117]. Basal platelet pH_i of Dahl rats correlated positively with plasma triglycerides and plasma cholesterol and the changes in microviscosity of the outer membrane leaflet might be involved in pH_i regulation [117,118]. The above findings were summarized in a review on the abnormalities of membrane function and lipid metabolism in hypertension, which was published in *American Journal of Hypertension* in 1999 [112].

Center for Cardiovascular Research

In 1999 the *Center for Cardiovascular Research* was established to combine the effort and expertise of leading Czech cardiovascular investigators. On this platform we have met an excellent newly formed research team of Dr. Luděk Červenka (Institute of Clinical and Experimental Medicine, Prague). He started his study in experimental nephrology and hypertension under the supervision of Dr. Jiří Heller [119,120]. In 1998 Dr. Červenka joined the laboratory of Dr. L. Gabriel Navar in New Orleans. There he studied the participation of renin-angiotensin system in the pathogenesis of two-kidney, one-clip Goldblatt hypertension with a special focus on renal functions [121-124]. He also paid the attention to the salt-sensitive hypertensive mice, in which bradykinin B_2 receptor was inactivated, showing that high-salt diet and angiotensin II infusion induces the increase in blood pressure [125,126]. Moreover, genetic inactivation of B_2 receptor led to the worsening of 2K-1C Glodblatt hypertension [127] (Červenka 2003). After the return to Prague, Dr. Červenka succeeded to establish a breeding colony of Ren-2 transgenic rats (harboring mouse renin gene), the breeding pairs being provided by Prof. Detlev Ganten and Dr. Michael Bader (Berlin). Thanks to a long-term fruitful cooperation with Prof. Herbert J. Kramer (Bonn) the experimental research performed in Ren-2 transgenic rats covered not only the contribution of particular RAS components such as angiotensin II receptor subtype AT_{1A} [128,129] or angiotensin 1-7 [130,131] but also the role of neuronal NO synthase [132,133] and oxidative stress [134-136] as well as the influence of salt intake [137,138] or anesthesia [139]. Importantly, they demonstrated substantial differences in plasma and renal angiotensin II concentrations depending on whether the animals were anesthetized or conscious. A considerable attention was paid to endothelin system. They demonstrated that non-selective ET receptor blockade reduced proteinuria and attenuated cardiac hypertrophy in homozygous TGR [140]. Later, they focused on selective ET_A receptor blockade both in heterozygous and homozygous TGR [141-143]. Another important topic of his research were CYP-450-dependent oxygenase products – epoxyeicosatrienoic acids (EETs) and 20-hydroxyeicosatetraenoic acid (20-HETE). They found higher urinary 20-HETE and lower EETs excretion in TGR as compared with normotensive HanSD, suggesting that the imbalance between pro-hypertensive and anti-hypertensive CYP-450 products contribute to hypertension in TGR [144]. The inhibition of 20-HETE formation and EETs degradation led to BP decrease [145,146]. Dr. Červenka also acquired CYP1a1-Ren-2 transgenic rats in which hypertension is inducible by xenobiotic indole-3-carbinole. Severe hypertension develops already two days following its administration and is accompanied by substantial body weight loss and cardiac hypertrophy [147]. Moreover, impaired renal autoregulation precedes the development of hypertension in this experimental model [148].

Since hypertension is largely caused by the enhanced constriction of small resistance arteries together with the attenuation of vasodilator mechanisms, we directed our research to both *in vitro* and *in vivo* abnormalities of vascular tone in various form of experimental hypertension. We also paid our attention to the accelerated growth of vascular smooth muscle cells (VSMC) isolated from SHR aorta and to the respective sex differences in this strain. We demonstrated a shorter doubling time in VSMC from male SHR compared to those from female animals [149,150]. VSMC isolated

from the aorta of male SHR proliferate more rapidly than those obtained from female SHR. Angiotensin II stimulation of VSMC growth was more pronounced in cells isolated from the aorta of male SHR compared to cells from female SHR [151]. Furthermore, we observed that the augmented $[Ca^{2+}]_i$ response to angiotensin II in male compared to female aortic VSMC was dependent on Ca^{2+} influx [152].

The balance of vasoconstrictor and vasodilator mechanisms

In 1987 we started to evaluate the contribution of various pressor systems to BP maintenance in DOCA-salt hypertensive rats [153]. Simultaneously, we were inspired by the papers of Dr. Haralambos Gavras and Dr. Bernard Waeber [154-157] who performed the acute blockade of particular vasoactive systems in conscious rats. Therefore, we adapted the experimental protocol described by Minami *et al.* [158] for the estimation of the contribution of three principal vasoactive systems (renin-angiotensin, sympathetic and nitric oxide) to BP maintenance. A sequential blockade of these three systems in conscious cannulated animals was used for this purpose. This gave us the opportunity to study the role of sympathetic nervous system (SNS) which seemed to be enhanced in various salt-dependent forms of hypertension [76,159,160]. Our first studies, which were performed in Dahl and HTG rats, indicated the sympathetic hyperactivity and relative NO deficiency in both forms of hypertension [161,162]. A comparison of BP response to the acute administration of tempol (superoxide dismutase mimetic) in young and adult Dahl rats suggested a greater involvement of reactive oxygen species in young salt hypertensive animals [163].

At that time Dr. Kuneš became a director of IPHYS and we established a valuable cooperation with Dr. Olga Pecháňová from the Institute of Normal and Pathological Physiology (Slovak Academy of Sciences, Bratislava). She introduced to us a model of NO-deficient hypertension elicited by chronic administration of non-specific NO synthase inhibitor L-NAME [164-166] and we started to examine this model using our techniques. One of our first joint papers [167] revealed the importance of sympathetic hyperactivity in this form of hypertension. We also reported that a considerable part of vasodilation persisting in L-NAME-treated rats can be abolished by the acute administration of the inhibitors of inducible NO synthase. Our further studies indicated a similarity of L-NAME-induced hypertension in immature and adult rats [169] and a possibility to attenuate the development of this NO-deficient form of hypertension by chronic N-acetylcysteine (NAC) administration [170]. Furthermore, we demonstrated that chronic NAC treatment augmented NO-dependent vasodilatation, whereas chronic captopril treatment reduced sympathetic vasoconstriction in rats with L-NAME-induced hypertension [171]. The importance of sympathetic hyperactivity in this form of hypertension was confirmed in our further study indicating the attenuated development of L-NAME-induced hypertension in rats pretreated with pertussis toxin inactivating Gi protein [172]. Within the frame of this cooperation we also studied the effects of chronic NAC administration on the development of genetic hypertension in young SHR (preventive study) [173] and on the maintenance of hypertension in adult SHR with established hypertension (therapeutic study) [174]. Finally, Dr. Kuneš upgraded the original concept that hypertension is a result of the interaction between genetic and environmental factors [175] by considering the significant role of epigenetic inheritance [176] (Fig. 4).

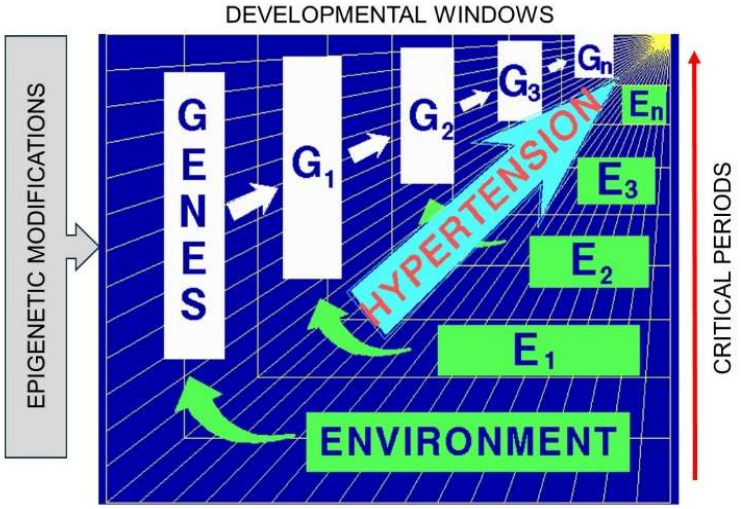

Fig. 4. Epigenetic and gene interactions with environmental factors during blood pressure ontogeny and hypertension development. E_1 - E_n represent environmental stimuli affecting expression of genetic information (G_1 - G_n) occurring in particular critical periods (developmental windows). Modified from our review [47].

Future perspectives

Another major profit from the collaboration with Dr. Pecháňová was the facilitation of the long-term work of several young Slovak colleagues in our lab – Drs Ludovít Paulis, Silvia Líšková, Mária Pintérová, Michal Behuliak and Michal Bencze. Together with the return of Dr. Ivana Vaněčková from the Institute of Clinical and Experimental Medicine (Prague) in 2010, this team was prepared for a further development of the Laboratory of Experimental Hypertension in IPHYS. The original direction of our research was modified towards new hypertensive models (Ren-2 transgenic rats) and new mechanisms in blood pressure control and hypertension development (role of endothelin, interaction of RAS and SNS, central and peripheral effects of angiotensin II, mechanisms of sympathetic hyperactivity, contribution of Ca^{2+} influx and Ca^{2+} sensitization, wire myography for the examination of conduit and resistance arteries). Thus, we were ready for a new chapter in the history of the Laboratory of Experimental Hypertension in IPHYS.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

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