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EDITORIAL

Systems Analysis in Hypertension: Complementary Role of Physiologists and Geneticists

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During the 13th International SHR Meeting (Prague, June 20-22, 2008) Paul Korner, Ted Kurtz and Michael Bader discussed the possibilities of mutual cooperation between physiologists and geneticists in the research of causes and mechanisms of genetic hypertension. Two years have elapsed and the genes important for the development of essential hypertension or genetic hypertension of the rat still remain to be identified.

In the present article "*The phenotypic patterns of essential hypertension are the key to identifying high blood pressure genes*" Paul Korner (2010) has summarized his ideas why defining the phenotype needs to be done adequately. The paper is based on his recent book (Korner 2007) about pathophysiological mechanisms important in essential hypertension and some types of genetic hypertension in rats. In this book he has compared the operation of the circulatory control system in the above disorders and under normal condition. Several major differences in their operation have been identified that are critical in the rise in blood pressure. Those initiating hypertension can be related directly to the major environmental factors important in essential hypertension, while the factors responsible for its progression depend on local factors and neuroendocrine changes acting on the vasculature and heart. His thesis is that these physiological differences characterize the important differences in the phenotype. He suggests that now the task of the geneticists is to identify the genes responsible for the differences in the systems operation, using approaches similar to those used in the study of ontogenetic development. It means to analyze the genome through the phenotype which is just the opposite to current approaches.

Paul Korner´s article explains why such an approach could be more advantageous than attempting to derive the phenotype from the genetic data – there are too many ambiguities in the present state of our knowledge. With overlapping counterregulation of numerous mechanisms there might be certain problems in the evaluation of true effects of various "BP genes". This is true not only for the dissection of known QTLs towards distinct genes but also for combining the physiological effects of disclosed SNPs. These problems also might cause the current effort of Allen W. Cowley and Howard J. Jacob who combined their knowledge in physiology and genetics to perform detailed genotyping and phenotyping of their hypertensive rat models (for review see Cowley 2006) using about 250 phenotypes in each rat studied (Moreno *et al.* 2003).

A considerable part of Korner´s article is devoted to the impact of the mechanisms that increase sympathetic neural activity to produce sustained elevation of blood pressure in mild to moderate hypertension. Our experimental data obtained in rats with various forms of experimental hypertension (ranging from genetically hypertensive SHR over salt-dependent Dahl rats and NO-deficient rats treated with L-NAME up to Ren2-transgenic rats) indicate a major role of sympathetic nervous system in the maintenance of high blood pressure (Fig. 1), although this system is the initial stimulus for hypertension development only in the first two models but not in the last two forms of experimental hypertension. This figure also shows a great importance of sympathetic vasoconstriction for the maintenance of systemic resistance and blood pressure even in models

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with a relatively high contribution of pressor effects of angiotensin II such as Ren-2 transgenic rats or L-NAME hypertensive rats.

During our discussions with Paul Korner we have often encountered "age" as a special phenomenon. It appeared in various forms such as "age of intervention", "ontogenetic development and its critical periods", "age of defect manifestation" etc. In all cases the importance of maturation or aging processes is based upon the inevitable passage of time, which seriously limits the reversibility of developmental changes, including those which are associated with pathophysiological processes in cardiovascular apparatus. Our recent reviews (Zicha and Kuneš 1999, Kuneš and Zicha 2006, Kuneš and Zicha 2009) attempted to evaluate the differences in the response of immature and mature organisms to various stimuli such as high salt intake or antihypertensive treatment based upon renin-angiotensin system blockade. These interventions always produce greater BP changes in young than in adult animals (Zicha *et al.* 1986, Zicha and Kuneš 1999). It should be mentioned that the plasticity of the immature organism, which is capable to develop numerous adaptations to the environmental stimuli, contrasts with the "rigidity" of mature organism which usually only compensates for the changes elicited by these stimuli. This could be partially ascribed to silencing of developmental genes which limits the extent of permanent remodeling of resistance vessels in adult rats, etc. (Korner and Bobik 1995). It should be kept in mind that most critical developmental periods can be found in early stages of the ontogeny (i.e. during prenatal and early postnatal life). Some of them are located in prepuberty because the antihypertensive treatment of young SHR can effectively lower BP for a long-time after drug withdrawal (Albrecht 1974, Harrap *et al.* 1990, Adams *et al.* 1990). The same is also true for gene therapy, e.g. the delivery of angiotensin type 1 receptor antisense in 5-day-old SHR induced long-term BP lowering, whereas this intervention performed in adult SHR caused only a transient BP decrease (Iyer *et al.* 1996, Katovich *et al.* 1999).

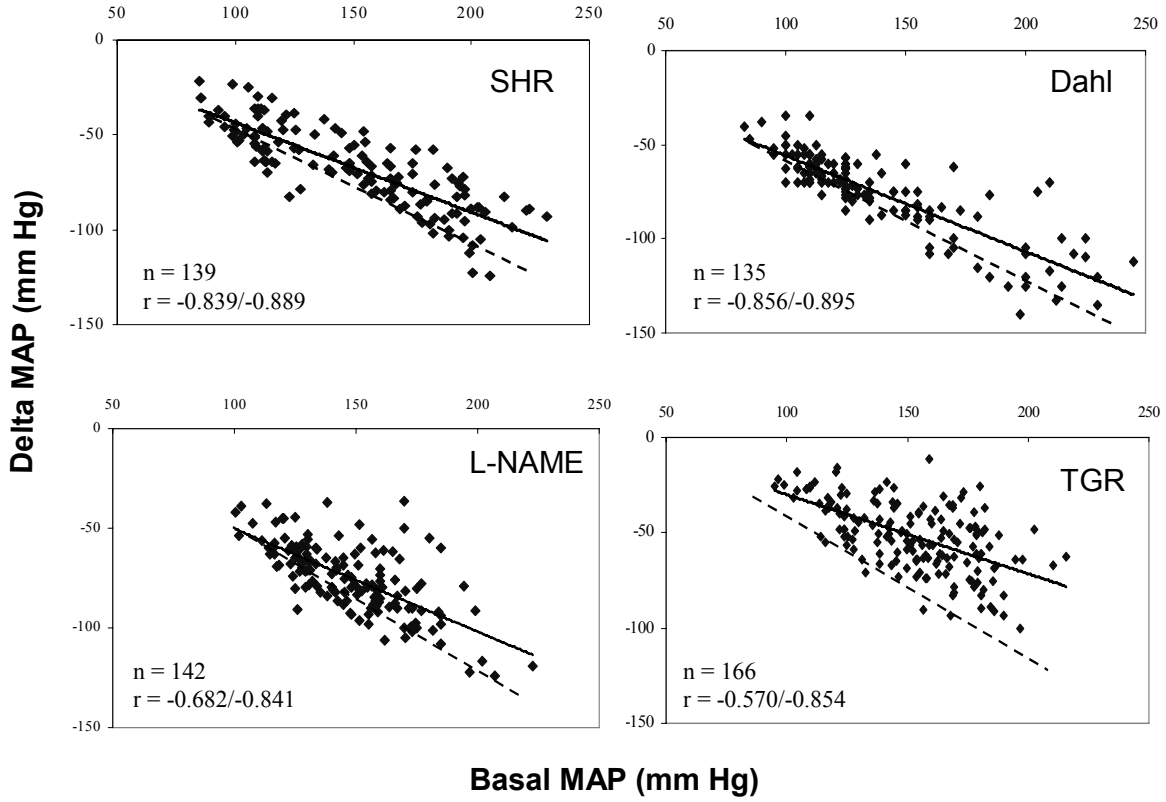

Fig. 1. The relationship of basal mean arterial pressure (MAP) to its sympathetic component (pentolinium-induced MAP decrease) in four different models of experimental hypertension. In each model normotensive controls as well as hypertensive animals at different stages of hypertension development and/or regression were used to obtain continuous distribution of basal blood pressure. Solid regression line and the first correlation coefficient always reflect the role of sympathetic vasoconstriction, whereas broken regression line and the first correlation coefficient are pertinent to BP effects of combined RAS and SNS blockade. The angle between both regression lines indicate the degree of angiotensin II participation in BP maintenance (high in Ren 2-TGR and L-NAME but small in Dahl rats).

The characteristic feature of pathophysiological processes occurring during the ontogenesis is a progressive evolution of minor changes induced in early stages of development into the pathological alterations fully manifested in adulthood and/or senescence. Barker´s hypothesis on the deleterious influence of "small babies/large placentas" might serve as an illustrious example. The study performed by Nilsson *et al.* (1997) in a large cohort of young Swedish boys revealed a small but significant BP difference which was dependent on the birth weight. The major influence of intrauterine malnutrition on BP were demonstrated in considerably older subjects (Barker *et al.* 1990, Law and Barker 1994). Unfortunately, the underlying mechanisms of "early programming" are still not fully understood, but the epigenetic changes should also be considered.

The complexity of ontogenetic development and gene-environment interactions (Kuneš and Zicha 2009) requires a close cooperation between physiologists and geneticists which might yield more efficient approaches for the detection of causes of important cardiovascular diseases. Of course, it remains to select the most plausible approach which should profit from the deep knowledge of complex pathophysiological mechanisms (obtained by means of systems analysis) rather than from a simple accumulation of genotypes and phenotypes.

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