Hypertension Research (2015) 38, 299–307

www.nature.com/hr

REVIEW

Environmental origins of hypertension: phylogeny, ontogeny and epigenetics

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Hypertension and renal parenchymal disease are intricately linked. Primary renal parenchymal disease can impact on sodium and volume regulation and lead to hypertension, while arterial hypertension can induce renal parenchymal injury and precipitate renal dysfunction. The examination for clues to the environmental origins of renal disease and hypertension necessitates an approach that integrates epidemiology, clinical medicine, developmental biology, environmental science and epigenetics, such that the manner in which genes and the environment interact can be better understood to pave the way for innovative management paradigms with regards to prevention, diagnosis and treatment. This review summarizes the extant literature and provides cogent arguments for the need to evaluate chronic adult onset disease models such as hypertension and renal disease from the modern perspective that takes into account prenatal exposures, the intrauterine environment and development, postnatal growth and transgenerational epigenetic modifications with their attendant future disease risk from the individual to the population level.
Hypertension Research (2015) **38,** 299–307; doi:10.1038/hr.2015.7; published online 19 February 2015

Keywords: Environment; epigenetics; phylogeny; ontogeny

INTRODUCTION

Essential or primary hypertension is a polygenic disorder, with genetic and environmental interactions driving its expression. Its diagnosis as a chronic medical disorder is based on defining arbitrary thresholds of blood pressure (BP) on the Gaussian distribution beyond which morbidity and mortality increase as evidenced by data of large-scale prospective epidemiological population studies.[1–4] Hypertension is aptly defined as 'the inability of multiple compensatory mechanisms involved in the control of BP to maintain the pressure within appropriate limits'.[5] The impact of restoration of BP to a range below the diagnostic cutoffs is obvious from the significant health benefits and improved survival when hypertension is adequately treated.[6,7]

The physiological control of BP is a function of hemodynamics, rheology, neural inputs and a myriad of vasoactive peptides and hormones.[8–11] Of these, the kidneys assume primary importance in the long-term control of BP.[12,13] Arterial BP and renal output of sodium and water form a classic negative feedback system. When this becomes dysfunctional, uncontrolled hypertension injures the kidneys, which in turn elevate the BP via positive feedback.[14]

The medical model of disease addresses hypertension by elucidating mechanisms or 'proximate' answers in terms of 'how' the causation came about. However, a broader perspective embracing the theme of natural selection as the supreme organizing principle is necessary to unravel the 'ultimate' answers as to 'why' hypertension occurs.

CLUES FROM EPIDEMIOLOGY

Interesting epidemiological findings ignite biologically plausible hypotheses regarding how the forces of nature have shaped the hypertension landscape. For instance, BP is found to be inversely proportional to altitude above sea-level. Residents at high altitudes show lower BPs despite having higher blood viscosity due to elevated hematocrit and secondary polycythemia from lower oxygen tension.[15] Evolutionary inference to the phenotypic mean differences between highland and lowland inhabitants, successfully explains why the BP should be lower at higher altitudes.[16]

A geographical distribution of prevalence of hypertension similarly occurs in relation to air temperature as climate produces a latitudinal cline in heat adaptation and hypertension susceptibility. Environmental biologists have postulated that BP should be negatively correlated to mean annual temperature worldwide.[17] This stemmed from the thesis of Carl Bergmann that homeotherms living in colder climates will be larger than those in warmer climates by virtue of thermal advantage of a smaller surface area to volume ratio of a larger body size, which in turn correlates positively with BP.[18,19] Local brief exposure to intense cold elevates BP transiently via vasoconstriction initially. Through the acclimatization process, the BP eventually normalizes among residents in colder environs, with consequent lower BPs compared with inhabitants in warmer climates. Although inconclusive, populations from hot environments are more susceptible to hypertension than those residing in cold climates, probably due to the inherent need by the former for increased vasomotor tone as a

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Received 13 July 2014; revised 2 December 2014; accepted 11 December 2014; published online 19 February 2015

defense against excessive vasodilatation to facilitate heat loss in response to hot weathers.[20] Ancestral adaptation to selective pressures during the migration of early humans out of Africa probably influenced the expression of genes influencing renal salt handling and arterial vessel tone and hence the differing susceptibility to hypertension between peoples.[20]

Geographic and spatial distribution of hypertension also appear to be mediated in part by dietary intake of potassium/sodium and the expression of genes governing vasoactive hormones, such as angiotensin II, aldosterone, natriuretic peptides and urinary excretion of sodium and potassium.[21] Closely related to dietary exposure is the role played by economic transition as reflected by the rising prevalence of hypertension in developing countries. The existence of a social economic status gradient with greater frequency of higher BP among urban-dwellers compared with their non-urban counterparts underscores this point.[22]

Demography and anthropology provide useful clues on ethnic and racial BP differences in any given environment. The angiotensinogen H1 haplotype is linked to higher levels of plasma angiotensinogen and hypertensive status in black families of African descent.[23] Angiotensin I-converting enzyme (ACE) single-nucleotide polymorphisms have yielded compelling data, such as the ACE4 'A' allele being associated with hypertension among the blacks.[24] Finally, epidemiology has unraveled a myriad of environmental factors, including vitamin deficiency, environmental toxins, nephrotoxic drugs, obesity and lifestyle factors such as psychological stress, sleep deprivation, smoking, salt/alcohol intake and occupational toxins, as likely contributory.

PHYLOGENY AND EVOLUTIONARY PERSPECTIVES

To understand the origin of hypertension in modern day humans, it is instructive to approach it from both evolutionary and comparative biology angles. Modern medicine stands to gain substantially by studying phylogeny as elegantly demonstrated by how physiology and systems biology are informed with respect to evolutionary principles that operate across the different vertebrates and non-vertebrates species.

The transition from a salt-plentiful marine aquatic to terrestrial life with salt paucity requires significant endocrine adaptation. Primitive bony fishes possess renal renin and juxtaglomerular cells during their early evolution but lack a feedback mechanism controlling renin release from the macula densa as the latter evolved later in vertebrate phylogeny probably stemming from their exposure to high sodium levels in the oceans since the primeval era. Amphibians and reptiles also lack a macula densa and extraglomerular mesangium, and avian kidneys have a transitional macula densa but no extraglomerular mesangium. The juxtaglomerular apparatus in birds is transitional between mammals and lower vertebrates.[25] In non-mammalian vertebrates, adrenocortical steroids act on several sites, including the gills, skin, nasal glands or salt glands in addition to the kidneys.[26] However, mineralocorticoids are mainly nephrotropic in mammals. As vertebrates expanded their habitats from aquatic to terrestrial environments, adaptation to life on land requires obligatory transformations in the osmoregulatory and cardiovascular systems to counter both dehydration and gravity and thus necessitates an elaborate renin–angiotension–aldosterone system (RAAS) to be evolved. Comparative biology of the RAAS reveals that the site of action of these vasoactive hormones was the systemic and preglomerular vasculature in primitive vertebrates. Indeed, it was only in the later stages of phylogeny that the RAAS act directly on renal tubules.[26] Hence, the available evidence suggests that the RAAS evolved with a close relationship to BP homeostasis.[25]

'Reverse' phylogenetics attempts to identify novel sodium-regulating and vasoactive hormones from comparative fish studies to provide insights into relevant regulatory pathways that deserve deeper scrutiny among humans.[27] Although nitric oxide is now the well-established endogenous vasodilator produced by the vascular endothelium, hydrogen sulfide has recently been shown to be a potent endogenous vasodilator. To aid our understanding of its phylogenetic significance and environmental trends, hydrogen sulfide was examined for vasoactivity in all vertebrate classes, including sharks, toads, alligators, ducks and humans. The data suggested that hydrogen sulfide is an ancient and versatile vasoregulatory molecule that switches its function according to species-specific and organ-specific homeostatic requirement depending on the nature of the habitat environment.[28]

Phylogeny is thus successful by providing better clarification and substantiating well the notion that hypertension is the consequence of maladaptive responses by homeostatic animals operating through highly conserved genes under selective pressures.

GENE–ENVIRONMENT INTERACTIONS AND BP REGULATION

Hypertension is the product of susceptibility genes in a mismatched environment. In this connection, the family history, age, gender, race, socioeconomic status, nutrition, salt intake, obesity, physical activity, traffic noise, psychological stress, smoking, climate and various toxins are all relevant. It is debatable if they operate independently or work via an overactive sympathetic nervous system.[29–32] In analyzing the contribution of nature and nurture, the kidneys turned out to be a predominant common mediator.

One of the key physiological functions of the kidneys is that of BP regulation via the mechanism of pressure–natriuresis.[33] Mathematical modeling demonstrated that this servomechanism would have an infinite gain, which means that it is capable of totally restoring BP to a homeostatic set-point at which sodium/water fluxes are balanced, over and above other biological subsystems contributing to BP control.[34] Any excess dietary sodium intake is prevented from raising the BP due to paralleled matching increase in the level of natriuresis consequential to increased blood volume and pressure. Although such a mathematical model explains the physiology well in a general sense, it is necessary to integrate into the model how adaptive genetic mutations may alter the renal tubular sodium transport and excretory capacity to account for observed differences in salt sensitivity between races. Hence, it is posited that appropriate genes must endow the acclimatized kidneys with capability of flattening the pressure–natriuresis curve characteristic and predisposing the early humans living in the African savannahs to sodium sensitivity.[35] Salt sensitivity as such refers to the elevation in BP from short-term manipulations that increase sodium intake thought to predispose individuals habitually on a high salt diet to hypertension. Such genetic drifts perpetuated during the out-of-Africa expansion and explain the origin of the risk of salt-sensitive hypertension among more African Americans than Caucasians in the modern environment (Figure 1). The efficiency of this pressure–natriuresis negative feedback loop is limited by the total available nephron glomerular filtration surface of the kidneys, a variable that may be both genetically and environmentally determined.[36] It is conceivable that the predicted capacity of the kidneys for pressure–natriuresis may be outstripped either by a very chronic excessive loading of salt or by absolute reduction in nephron number.

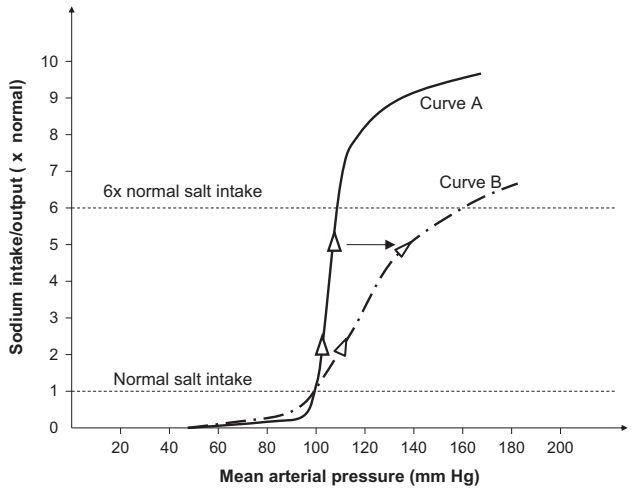

Figure 1 The pressure–natriuresis relationship allows for a tight control of BP within a narrow physiological range appropriate for cardiovascular health and survival despite large increases in salt intake, which is approximately matched by equal amounts of sodium excretion, as illustrated by curve A (solid line). For a salt-sensitive individual (curve B, dotted line) endowed with ancestral genetic modifications selected for a higher thresholds for sodium excretion and elevated capacity for sodium conservation, even modest intake of salt will result in a significant increase in arterial BP.

THE PATHOGENIC ROLE OF SALT AND OTHER DIETARY FACTORS

Sodium has long been suspected as an etiology of hypertension since a century ago.[37] Animal studies for years have also consistently shown that high salt intake induced elevation in BP.[38] Salt began as a trivial component in the diet of prehistoric humans for millennia. Populations around the world who consume large quantities of salt suffer from high rates of hypertension, compared with hunter-gatherer tribes subsisting on diets low in salt.[39] It is not surprising therefore that hypertension is an esoteric disorder in societies on low salt diets.[40,41] Research subsequently proved that lowering the intake of salt also decreased BP.[42–44] Unfortunately, sodium consumption has been creeping steadily upwards, from 2300 mg daily in the early 1970s to about 3300 mg just a decade ago.[45] The average hunter-gatherer's sodium intake is only about 20 mg in stark contrast.[46] The human body only requires about 180 mg per day to replace losses in perspiration and urinary and gut losses.[47] Increased sodium in the circulatory system induces vasoconstriction via a recently discovered mechanism mediated by endogenous ouabain and the sodium–calcium exchanger of vascular smooth muscles, which further raises BP and reduces tissue perfusion.[48]

From an evolutionary standpoint, the genetic variants which produced salt-sensitive phenotypes that favored salt retention by an avid RAAS among the early human beings who survived in the hot, dry conditions were positively selected. Although salt sensitivity confers a survival advantage, it lowers the threshold for BP elevation with salt excess (Figure 2). As a corollary, the black Africans serve as a good model of salt sensitivity as a risk for hypertension. Their ACE polymorphisms and angiotensinogen mutants have so evolved as to render ACE inhibitors far less effective as antihypertensive agents than diuretics monotherapy in line with prediction based on the survival advantage conferred by natural selection in people living in arid, hot climates.[49] Lower renin activity among African Americans increases distal tubular delivery of sodium and tubular hyperperfusion of the macula densa, which could also explain the greater antihypertensive effectiveness of thiazide diuretics compared with either beta-blockers or ACE inhibitors in this racial group.[50–54]

Dietary intake of potassium, calcium, magnesium, polyunsaturated fatty acids and alcohol are also relevant.[55–56] BP has long been found negatively correlated with potassium.[54] Similarly, adequate polyunsaturated fatty acid intake has been shown to very modestly lower BP, probably via prostaglandin pathways.[55] A significant correlation exists between mean daily alcohol intake and BP; in particular, in most alcoholic hypertensives whose daily consumption exceeded 80 g, BP normalized with abstinence and increased again following resumption of drinking, showing a definite dose–response effect.[56,57]

Diseases of civilization often have their developmental origins based on the 'thrifty genotype' hypothesis by late James Neel.[58] In a similar vein, 'thirsty genes' conserved by our hunter-gatherer ancestors who survived in situations of salt scarcity might have conferred a survival advantage to defend against many volume-depleting states such as profuse perspiration, hemorrhage or diarrheal illnesses commonly encountered in austere environments.[59] Our present salt- and water-conserving genetic legacy is thus evolutionarily derived from ancestral hominid origins who successfully withstood the privation of terrestrial life on arid and salt-scanty inlands by natural selection. Hence, the 'hypertensive' genes that shaped the phenotype of the fittest are clearly an adaptation optimizing the organism for survival in the challenging ecological land niche. Expectedly, our ancestors who lived during the era before salt becomes excessive would not have been afflicted by hypertension. Indeed, historical records suggest that hypertension is very much a modern day disease unveiled by the high salt content of our present day diets.[60,61]

RENAL SIZE AND NEPHRON NUMBER

Allometric scaling has predicted a coherent relationship between body weight and renal size such that its allometric constant lags behind the allometric constant of blood volume and body size.[62] Accordingly, a renal functional deficit becomes apparent when linear body growth is propelled to the genetic limits in the nutritionally enhanced environment following cessation of further kidney growth at puberty or when intrauterine growth restriction retards kidney growth proportionally greater than the overall body size.[63] The theory of allometry predicts that hypertensive people will have glomeruli, tubules and kidney sizes smaller than a population of normotensives.[64]

In 1988, Brenner *et al.*[65] proposed that individuals endowed with fewer nephrons would be at a higher risk for development of hypertension later in life. On average, a human kidney has about 8 44 000 nephrons.[66] A reduction in size of glomeruli and nephron number sufficient to impact on glomerular filtration surface area will predispose the affected individual to alteration of the BP set-point and hypertension. Since the 1930 s, the association between low nephron number and hypertension had already been described.[67] Series of human autopsies confirmed that the Australian aborigines who have the lowest number of nephrons are also the group with the highest rates of renal failure and hypertension.[68] Postmortem three-dimensional stereology of those with primary hypertension compared with normotensive matched controls showed significant correlations between low nephron number and hypertension, with the hypertensive group with fewer nephrons (median: 7 02 379 vs. 14 29 200).[69]

Munich–Wistar–Fromter (MWF) rats with inherited nephron deficit compared with their wild-type Wistar rat controls spontaneously develop hypertension in the course of their growth.[70] It has been shown that the insulin-like growth factor (IGF) system is crucial in nephogenesis and that both insulin-like growth factors I and II availability are deficient during the critical period of kidney

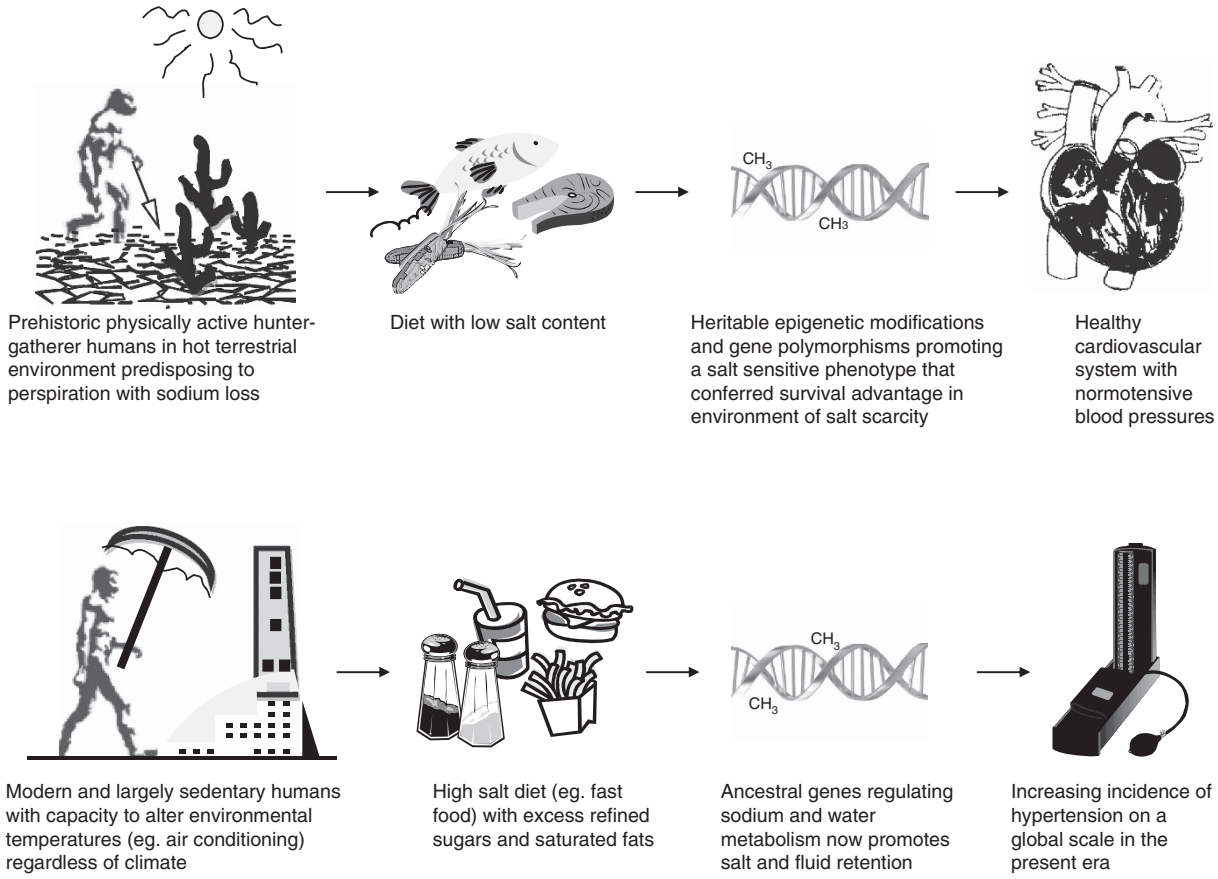

Figure 2 Schematic illustrating the manner of gene–environmental interactions that led to the conservation of heritable genetic changes favoring a salt-sensitive phenotype that predisposes to hypertension in a mismatched environment of sodium excess in the current age.

development in MWF rats, leading to lower nephron numbers.[71] In a sheep model of glucocorticoid-induced hypertension, prenatal dexamethasone exposure during the nephrogenesis period when compared with a controlled group resulted in hypertensive sheep at 7 years of age, with significantly lower total nephron number associated with glomerulomegaly as determined by unbiased stereology.[72]

Nephron number and glomerular size is negatively correlated with age and positively correlated to kidney mass.[73] That BP gradually increases with age could therefore be partly explained by a progressive decline in nephron number in addition to arteriosclerosis. Metabolic rate correlates with body surface area and the latter correlates better with kidney mass and total glomerular volume but not to the number of glomeruli.[74] Thus, kidney filtration capacity adapts to metabolic demands by altering the glomeruli size instead of changing glomerular number.[75] Such adaptation favors hyperfiltration injury and glomerulosclerosis with consequent risk of nephron loss.

Others have shown that reduced nephron number is an essential but not a sufficient condition for nutritionally induced hypertension. Fetal nutrient deficiency in the form of asymmetric growth restriction results in redistribution of blood flow from organs such as the skeletal muscles, liver and kidneys to organs critically important for fetal survival such as the heart and brain. The kidneys at this vulnerable period of growth restriction suffer from a permanently reduced number of nephrons. Following accelerated postnatal growth, the increased body mass with consequent elevated excretory load becomes excessive for the reduced excretory capacity of the kidneys, which therefore undergo intrarenal compensatory mechanisms of glomerular and tubular hypertrophy with single nephron hyperfiltration and intrarenal renin–angiotension system activation, setting the stage for development of hypertension.[76]

INSIGHTS FROM ONTOGENY AND EPIGENETICS

The complex gene–environment interactions as the pathway for development of hypertension have much support from studies of ontogeny. Embryologic and antenatal events that restrict fetal growth have been shown to impair nephrogenesis, and the price of that low nephron endowment is the heightened risk of hypertension and renal disorders in later life. Much remains to be learned about how including the postnatal environment nutrition affects nephrogenesis. The connection between the long-term effects of early childhood nutrition on cardiovascular and renal disorders in late adulthood deserves more investigation in this age of epigenetics.

Accordingly, the 'thrifty phenotype' hypothesis of Hales and Barker[77] proposes that the plasticity of the fetal genome facilitates *in utero* programing via epigenetic mechanisms to allow the fetus developing in an antenatal environment of scarcity to anticipate the environment it will encounter postnatally. Intrauterine growth constraint has been shown in both humans and animals to lead to their newborns having fewer and smaller glomeruli, which impair the renal pressure–natriuresis servomechanism by operating it at a higher BP range.[78] Barker *et al.*[77] demonstrated an inverse correlation between birth weight and incidence of hypertension and cardiovascular disease.

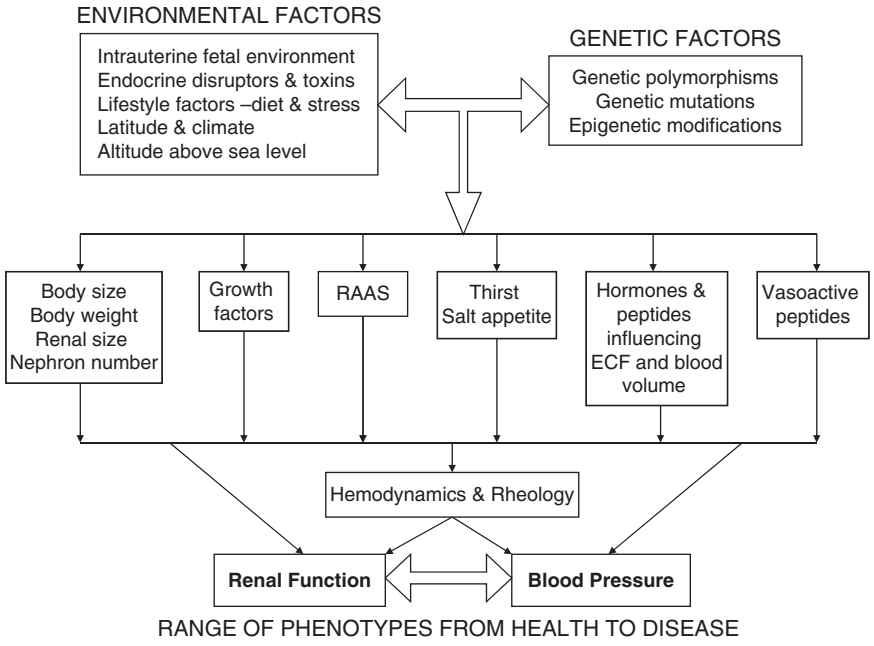

Figure 3 Summary of the nature of environmental interactions with genetic factors that impact on kidney function and BP which may in turn influence the risk to development of renal disease and hypertension. RAAS, renin–angiotensiin–aldosterone system, ECF, extracellular fluid.

The well-established rapid catch-up growth observed among intrauterine growth-restricted individuals with smaller kidneys during postnatal development may amplify the discrepancy between the allometric proportions of somatic size to the kidneys, which may result in dysfunction of the pressure–natriuresis in physiological blood volume regulation and therefore correlate with hypertension in later life. Together with the iming of onset of the pubertal growth spurt, the growth trajectories during childhood and adolescence can influence BP in adulthood in the future.[79]

Fetal undernutrition thus has a lasting impact on BP programing as shown by the associations between birth weight and cardiovascular disease supported by animal experiments and human data. Yet, the risk for hypertension in relation to birth weight may be more complex than earlier suspected as suggested by a recent meta-analysis. Individuals born at the other extreme, namely high birth weight, are also prone to hypertension during childhood. Enigmatically, as they grow older, their susceptibility to hypertension paradoxically becomes lower than those born with normal birth weight.[80] Maternal diet may be a crucial factor as this probably influences intrauterine availability of fetal nutrition. A recent murine study showed that maternal low protein diet during gestation apparently has the capability of programing reduced nephron number and hypertensive effects in offsprings up to the second generation. This trans-generational programing is likely the result of stable, heritable epigenetic changes induced by maternal diet.[81] To resolve how much does genetics as opposed to intrauterine environmental factors play in fetal origin of hypertension, twin studies offer a unique opportunity to dissect their relative contributions to birth weight and cardiovascular disease risk. In one twin cohort, it was found that low birth weight was associated with insulin resistance, lower high-density lipoprotein and shorter height within both the dizygotic and monozygotic twin pairs with discordant phenotypes, suggesting these associations are partly independent of genetic factors.[82] Relevant to this is the finding of greater aortic intimal media thickness among fetuses with intrauterine growth restriction compared with those with fetal weight appropriate for gestational age. When followed up postnatally, the systolic BP of those in the intrauterine growth restriction group was significantly higher than the appropriate for gestational age group, and this correlated well with the prenatal and postnatal aortic intimal media thickness.[83] The late effects of childhood nutrition likely have a role but remained unclear. Overnutrition may be detrimental as a rat model had demonstrated that early postnatal overfed rat pups enhanced postnatal nephrogenesis with a 20% increase in glomerular number but paradoxically led to increased proteinuria and glomerulosclerosis and systolic hypertension. Evidently, there must be other reasons apart from reduced nephron number alone that influence BP.[84]

Environmental influences, including the 'intrauterine climate' and the maternal–fetal interface, may interact adversely with the kidneys to promote the expression of hypertension in adult life. Experimental evidence clearly shows that the early nutritional perturbations in the intrauterine environment can have lasting epigenetic programing effects on cellular and organ development, which then results in obesity and hypertension in adult life. Research now focuses on mechanisms of organ dysfunction and on refining the understanding of the interaction between common elements of adverse perinatal conditions, such as nutrition, oxidants and toxins exposures, taken together as part of the entire range of environmental factors that can interact with the genetic makeup to cause hypertension (Figure 3). Modulating developmental programing offers the hope of a critical window of opportunity to reverse programing and prevent or reduce related adult-onset diseases. The notion of far reaching effects of dysfunctional or compromised maternal nutrition and health on the perinatal milieu that drives the fate of vasculogenesis and nephrogenesis is increasingly appreciated.[85] Metabolic outcomes and changes in renal function and hypertension are correlated to the rates of antenatal and postnatal growth. Ontogeny as such reveals invaluable clues regarding the pathogenesis of perinatal programing and provides opportunity for intervention at the prenatal stage for prevention of hypertension, renal and metabolic disorders.

ETIOPATHOGENESIS AND MOLECULAR MECHANISMS

The molecular mechanisms underlying the etiopathogenesis of a disorder with an environmental origin would expectedly involve fundamental biochemical interactions with the genome. In this scheme, environmental factors can exert their profound impact on gene expression via epigenetic modifications, which represents stable, heritable yet potentially reversible modifications without any mutations of the genetic sequence *per se*. DNA methylation, histone modifications, microRNA and genomic imprinting are the epigenetic processes that typically govern the environmental–genetics nexus. In contrast, actual mutations causing hypertension are probably very rare, such as exemplified by hypertension from a gain-of-function mutation of the aldosterone receptor.[86] Another example would be the mutations of the WNK kinases due to large intronic deletions or missense mutations of the WNK family of serine–threonine kinases affecting sodium–potassium homeostasis at the distal nephron, causing a monogenic hypertension with Mendelian inheritance.[87]

The whole range of systems that regulate BP over the short, intermediate and long term might be subjected to any of these epigenetic changes. BP is a function of cardiac output, blood volume and vascular resistance. Cardiac output is dependent on myocardial contractility and autonomic nerve discharge, while blood volume is dependent on sodium and hydration status together with systems that control fluid balance such as the kidneys that act according to sophisticated endocrine signals, such as the mineralocorticoids and glucocorticoids. Indeed, an epigenetic pathway for aldosterone signaling has been identified whereby the control of epithelial sodium channel-a (ENaCα) subunit gene expression in the nephron collecting duct is affected by histone H3 Lys-79 methylation of chromatin associated with the ENaCα promoter, which may be implicated in renal fibrosis and hypertension.[88] It is likely that many more dysfunctions of the local and systemic components of BP regulation leading to hypertension will eventually be found to have an epigenetic basis at the gene–environment interface.

OBESITY, INSULIN RESISTANCE AND URIC ACID

Obesity, metabolic syndrome and type 2 diabetes are conditions now understood to have their origins partly rooted in early developmental history. The association between gout, obesity, diabetes, kidney disease, hypertension and cardiovascular disease has been appreciated as early as the 1800s.[89] Notably, humans have higher serum uric acid levels than most other mammals due to mutational silencing of the uricase gene during hominoid evolution in the Miocene epoch between 8 and 24 million years ago, an event postulated to confer a selective advantage through BP homeostasis mediated by uric acid in low-salt environments.[90] Splice variants of the SLC2A9 gene, which encodes a combination high-capacity urate transporter and high-affinity glucose-fructose transporter, have been found to contribute to 5–10% of serum uric acid concentrations in *Homo sapiens*.[91] This has important bearings because of the ever increasing global consumption of refined sugar (sucrose) and fructose since the past two centuries in the developed world that has been linked to higher serum uric acid and the metabolic syndrome.[92] Fructose metabolism results in a rapid decline in ATP and increases uric acid production.[93] High-fructose diet in humans has been shown to induce both hypertension and many features consistent with the metabolic syndrome.[94] As a corollary, decreasing uric acid levels can reverse hypertension and many features of the metabolic syndrome.[95] Fructose-induced hyperuricemia might therefore be an important dietary mechanism accounting for the rising incidence of hypertension worldwide from a public health standpoint.[95] Recent experimental and clinical evidence now strongly suggest that elevated uric acid may lead to hypertension.[96–99] As hyperuricemia has been shown to precede the development of hypertension, it is no longer assumed to be a consequence of hypertension but rather as an antecedent factor that has a crucial role in the pathogenesis of hypertension.[100] Its well-documented antiangiogenic effects implies it might be responsible for reduced nephron number and low birth weight in babies born to mothers with preeclampsia and hyperuricemia based on the fact that uric acid transfers freely between maternal and fetal circulation.[101]

ENDOTHELIUM AS ENVIRONMENT–ENDOCRINE INTERFACE

The endothelium lining the blood vessels elaborates a host of paracrine vasoactive factors, which serve as major determinants of vascular structure and function.[102] Vasodilatory substances, including nitric oxide and prostacyclin, and vasoconstrictor substances such as thromboxane A2 and endothelin-1 are finely modulated by the endothelium, which in turn alters vascular tone and BP.[103] As blood is a major carrier of exogenous and endogenous molecules, its constant contact with the endothelium as it courses through the 1 00 000 km of vasculature makes the endothelium one of the largest endocrine organ that interfaces between the external environment and the multi-organ systems of the human body. Vascular physiology, which contributes significantly to BP regulation, is itself a very complex area that is controlled by the endothelium, smooth muscles of the vessel wall and a whole array of cells, hormones and cytokines (for example, adrenomedullin, natriuretic peptides (atrial natriuretic peptide/brain natriuretic peptide/C-type natriuretic peptide), vasopressin (arginine vasopressin), endothelin, angiotensin II, prostaglandins) operating via autocrine, paracrine and endocrine pathways, mostly via agonist–antagonist mode of action that allow fine-tuning of BP to accommodate a multitude of environmental challenges ranging from mundane to austere situations.[104]

Endothelial dysfunction is associated with impaired nitric oxide synthase (endothelial nitric oxide synthase) activity and endothelium-dependent vasodilatation.[105,106] This contributes to elevations in BP, which further impairs endothelial function by positive feedback. Endothelial dysfunction therefore has a critical role in the development of hypertension. Adverse fetal nutritional supply affects endothelial function and increases hypertension risks through fetal programing. DNA methylation, posttranslational histone modification and chromatin-based mechanisms have been shown to influence endothelial function by affecting the expression of endothelial nitric oxide synthase.[107,108] This area of science is still very much in its infancy and is likely to grow rapidly in importance as the complex functions of the endothelium are dissected with the cutting edge of epigenetics.

ROLE OF ENDOCRINE DISRUPTORS

Endocrine disruptors are exogenous chemicals that when absorbed into the body mimics or blocks hormones and disrupts normal body functions. This can occur though stimulation or suppression of hormone synthesis, alteration of hormone concentrations and kinetics, changes of hormone regulation, distribution and metabolism and thereby affecting the functions that endogenous hormones control. There are innumerable ways that endocrine disruptors can interfere with gene expression and therefore fetal development, which depend exquisitely on endocrine signals in the hormonal milieu of the intrauterine environment. Nephrotoxic substances can inflict permanent lesions to the developing kidneys of the fetus and lead to chronic proteinuria or even hypertension.[109]

Multiple lines of evidence suggest that endocrine disruptors may be responsible for much of the burden of chronic maladies that plague mankind, including cardiovascular disorders such as hypertension, obesity, diabetes, reproductive failure and cancer.[110] Environmental endocrine disruptors such as dioxins and polychlorinated biphenyls (PCBs) have exceptionally prolonged half-lives of 7–10 years in the human body that have been shown to interfere with estrogen metabolism. Maternal exposure to endocrine disruptors has been found to correlate with placental levels following delivery, with potential detrimental long-term sequelae to the fetus.[111] *In utero* exposure to environmental PCBs and dioxins have been found to be negatively associated with birth weight and postnatal growth until 3 months of age.[112] As well, the level of PCBs is positively correlated to BP.[113] This finding is supported further by NHANES 1999–2002 in which 7 of the 11 PCBs were found significantly associated with hypertension. The strongest adjusted associations with hypertension were found for dioxin-like PCB 126 and PCB 118, indicating that elevated PCBs is an independent risk factor for hypertension.[114]

The growing worldwide concern that endocrine disruptors can influence epigenetic mechanisms, chromosomal stability and gene expression implies the urgent need to evaluate the impact of environmental pollution on hypertension, especially in terms of the developing fetus, disease onset in adulthood and possible heritable epigenetic changes to affect hypertension risks to offspring in the future. Environmental exposure to persistent organic pollutants has been determined to be associated with changes in global DNA methylation levels in a human population.[115] Moreover, endocrine disruptors can modulate epigenetic programing of the germ line during embryonic development and not only affect the developing offsprings but also transmit transgenerational adult onset disease.[116]

CONCLUSIONS

Hypertension and renal disease are both highly prevalent human afflictions with devastating morbidity and mortality. Their pathogenetic basis is now gradually understood to involve intricate pathways linking the environment with the genome via epigenetic mechanisms that are recently being unraveled. The hope is that the better insights of the environmental origins of hypertension and renal disease will allow us to explore novel ways to target these disorders and reduce the toll they currently exact on our species.

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