Evolution and Hypertension

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Editorial

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Evolution by natural selection is the supreme organizing principle of biology, but it has not been widely applied in medicine.[1] Medicine has historically been concerned with mechanistic, or "proximate," answers to questions of how diseases develop and cause pathology. In contrast, evolutionary, or "ultimate," questions, frequently ask "why" structures or functions are as they are.[2] A full explanation of a disease should ideally address both, and what follows is a review of aspects of proximate and evolutionary thinking in hypertension.

Pressure–Natriuresis: The Key Mechanism of Hypertension

As animals evolved, body size increased, and delivery of nutrients to cells came to exceed the range of diffusion. Simple systems capable of supporting cellular metabolism arose, and natural selection went on to shape our staggeringly complex, highly integrated cardiovascular system. Contemporary cardiovascular research is almost exclusively concerned with detailed descriptions of the proximate features of cardiovascular function and structure, and we now understand many aspects in exquisite detail. Blood pressure, however, cannot be reduced to the individual elements of the circulation. It is a function of all of them acting in concert; it is an emergent property of the entire system.

All hierarchically organized biological systems have higher-order emergent functions that depend on, but are not predictable from, the structures and functions of lower levels,[3] and because emergent properties are lost when a system is disaggregated, integrative physiology is critical to understanding blood pressure regulation. The most comprehensive description of cardiovascular system physiology and blood pressure control is the systems analysis mathematical model developed by Guyton et al,[4] which proposes renal pressure–natriuresis as the dominant regulator of blood pressure.

The relationship of chronic pressure–natriuresis to the regulation of blood pressure level has been the focus of a great deal of research, and we now understand some of the regulatory mechanisms (reviewed in Reference 5). Pressure–natriuresis is a classic negative feedback control system: when arterial blood pressure increases, renal output of sodium and water increases above intake and blood pressure falls. Guyton et al[4] proposed that this feedback mechanism has infinite gain, that is, it completely restores blood pressure to a "set point" at which sodium and water intake and output are balanced. Renal pressure–natriuresis is, therefore, the dominant mechanism controlling the set point about which blood pressure is regulated, and although there are many other short-term blood pressure regulators, the infinite gain of renal pressure–natriuresis feedback trumps all other subsystems over the long-term. Understanding how the normal set point of pressure–natriuresis rises to support hypertension requires consideration of additional questions of biological explanation.

What Role Does Adaptation by Natural Selection Play?

Evolution by natural selection shapes phenotypes adapted to improve the fitness of organisms, that is, features that increase the chance that individuals will pass on their genes to their descendants.[6] Natural selection is a subtle and powerful force, but some of its results on first consideration may seem to be maladaptive, including the preservation of genes for hypertension. This perception arises from how we interpret the deleterious effects of genes in our medical model: those that harm us must be mistakes of natural selection.[7] But it is usually wrong to focus on the disease itself as the target of selection.[7] Hypertension is a prototypical "disease of civilization" that is only expressed in current milieus; it simply did not exist in earlier times.[8] Natural selection must, therefore, have acted on something else that optimized fitness in the ancient environment, and hypertension is only now an undesirable pleiotropic effect of the preserved genotype: genes conferring susceptibility to hypertension were not directly selected for that phenotype.

Exactly what was selected is not clear. Most evolutionary explanations of diseases of civilization converge on the late James Neel's "thrifty genotype" hypothesis.[8] Neel's now familiar and widely accepted argument is that "thrifty" genes contribute to reproductive success by improving an organism's ability to conserve nutritional resources obtained in times of surfeit, thereby favoring survival during times of want. Natural selection shapes organisms to function within a particular set of environmental conditions, but environments change, and in the case of thrifty genes, the modern environment now promotes the development of the metabolic syndrome.[9] Because organisms adapt to the totality of their environment, their ecological niche, and because the extraordinarily flexibility of human behavior has created a broad and deep niche, identifying and measuring the novel environmental factors that promote hypertension is challenging. Investigators using an ecological approach that exploits cross-cultural environmental diversity have correlated a number of environmental elements with hypertension. Because of its importance to survival, documentation of a strong drive for

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sodium acquisition in our hominid ancestors,[10] its markedly increased availability in modern times, and its key role in blood volume regulation, sodium is the best studied of the environmental factors.[11–13]

Pressure–natriuresis regulates blood pressure around a set point and usually prevents dietary sodium excess from raising blood pressure: even when sodium intake is extraordinary, blood pressure responses can be quite modest.[14,15] Sodium sensitivity results from a flattening of the pressure–natriuresis relationship, reflecting altered renal sodium handling from either intrinsic renal processes or extrarenal factors that impact renal sodium excretion. Genes are one potential source of variation in renal sodium excretory capacity, and mutations affecting renal tubular sodium transport cause several syndromes in which hypertension is a prominent feature.[16] These uncommon mutations are clearly deleterious and seem certain to decrease fitness, but genetic differences that produce effects on renal tubular sodium reabsorption may contribute to essential hypertension. If such genetic variants mediating differences in renal sodium handling resulted in phenotypes subject to natural selection, the intensity of that selection could have created the substrate underlying interindividual and interpopulational differences in the predisposition to hypertension.

The "Sodium Hypothesis"

Some 3 decades ago, Gleiberman[11] proposed that natural selection for sodium conservation in the hot, dry savannah climate into which humans first emerged could have resulted in sodium avidity that today is maladaptive. In essence, she proposed a "thrifty genotype" for sodium. As humans migrated out of Africa, selection pressure for sodium conservation would be expected to decline in the cooler, wetter climates of the northern latitudes. However, ancestral sodium-conserving genotypes would be expected to persist as the result of genetic drift. If genes originally selected for sodium conservation changed the set point of the renal pressure–natriuresis to a higher blood pressure range when expressed in an environment of sodium abundance, individuals harboring such genotypes could be at increased risk of developing hypertension.

The best evidence that chronic sodium deprivation prevents and chronic sodium excess permits the development of hypertension comes from observations of differences in the prevalence of hypertension in populations living in areas of low and high sodium availability.[11,17] Experimental evidence from trials of dietary sodium restriction also generally supports the sodium hypothesis: African Americans have a higher prevalence of sodium sensitivity than whites. One of the problems with studies of dietary sodium is that most do not extend beyond a week, probably too short a time to see the full expression of the effect of sodium on blood pressure.[18]

Natural Selection and Sodium-Conserving Genotypes

Recent genomic studies have provided strong support for a role of natural selection for sodium conservation in Africans. Several allelic variants of genes involved in sodium handling can be characterized as sodium conserving or heat adapted, including the −6A allele of the promoter of the angiotensinogen (AGT) gene,[19] the 825T allele of the GNB3 gene, the 47A and 79C alleles of the β2-adrenergic receptor gene, the −946G allele of the epithelial sodium channel α-subunit gene,[20] and the CYP3A5*1 allele of the CYP3A isozyme 5 gene.[21] These variants show strong latitudinal clines in which the sodium-conserving alleles, the ancestral variants, are much more prevalent in African populations living near the equator and less so in populations from northern regions or the New World. Genomic studies of 2 of the derived variants, AGT −6G and GNB3 825C, show that they are flanked by genomic regions of broad linkage disequilibrium and low haplotype diversity.[19,21] These "signatures of natural selection" suggest that the new alleles arose recently and were exposed to positive selection and, by implication, that the originally adaptive ancestral alleles became harmful to those individuals who migrated to cooler climates.[19,21]

Precisely how the derived alleles were selected is unknown. It has been suggested that by predisposing mothers to preeclampsia, the ancestral alleles could have negatively impacted fitness, but such a scenario would probably favor genetic drift rather than positive selection for derived alleles.[20,22,23] Drift may explain some of the observed variation in AGT polymorphism frequency (eg, the high prevalence of the derived allele in the Hema population of Africa), but because the frequencies of other AGT alleles are not increased, the evidence does not support a critical role for genetic drift in other regions of the AGT gene.[19] The most parsimonious interpretation of the genomic data is that either derived alleles were subjected to relatively strong and rapid selection or that the ancestral alleles were strongly selected against. The residual ancestral allele frequencies in younger populations could reflect the relatively short time since the African exodus, heterozygote advantage, or gene flow from the older populations. Regardless of the reason for the latitudinal gradients, rates of hypertension and sodium sensitivity are generally higher in individuals carrying the ancestral alleles in the modern environment and, thus, are compatible with a gene-by-environment interaction of ancient alleles and modern conditions as predicted by the "sodium hypothesis."

Mitochondrial DNA variants may also contribute to a diathesis to hypertension. Regional geographic variation in mitochondrial DNA sequences suggests that natural selection may have favored haplotypes that permitted cold adaptation, and, as argued for the nuclear DNA polymorphisms described above, the selection of cold-adapted genotypes might result from a deleterious effect of heat-adapted African haplotypes in the novel environment of the north.[24] Although less-intensively studied than nuclear DNA polymorphisms, there are suggestions that mitochondrial DNA polymorphisms may explain part of blood pressure variation.[25–27]

The "Slavery Hypothesis"

Wilson and Grim[28] and Grim et al[29] proposed a "slavery hypothesis" explicitly positing a role for a selective advantage of sodium-conserving genotypes now rendered maladaptive.[28,29] Historic records of the Middle Passage of the slave trade describe meager diets, certainly deficient in sodium, and

hot, filthy quarters in which sweat and infectious diarrhea resulted in continuous sodium loss. The ability to conserve sodium could have been critical to survival during the Middle Passage, so that selection can plausibly be invoked as a mechanism preserving genes responsible for phenotypes capable of the most vigorous antinatriuretic responses. Differential mortality may, therefore, have resulted in a genetic bottleneck, which could have markedly reduced genetic diversity and increased the frequencies of sodium-conserving alleles in survivors. Those Africans who survived and reproduced would have passed those sodium-conserving genotypes to their offspring, establishing a genetic predisposition for renal sodium avidity that now leads to excessive sodium retention and sodium-sensitive hypertension in modern day African Americans.

Without entering into the debate about whether it is correct,[30] the hypothesis is testable and, therefore, useful. Studies of the relationship of sodium retention to sodium sensitivity in blacks and whites have been inconclusive,[31–33] and genomic testing of patterns of diversity in sodium-conserving genes may be a better way of characterizing ethnic differences in sodium sensitivity arising from selection during the Middle Passage. Because intense recent selection should have left the genomic "signatures of selection," or bottlenecking, ancestral allele frequencies would be expected to be greater in African Americans than native Africans. Whether such signatures will be detectable remains to be seen. The relatively high allele frequencies of sodium-conserving alleles in Africans and the extensive genetic heterogeneity of West African populations may obscure recent changes in frequencies in African Americans, and the effects of outbreeding and genetic admixture will present further difficulties. Nonetheless, seeking evidence of recent selection is one way of testing the slavery hypothesis. Other approaches, such as mathematical modeling of the genomic effects of a genetic bottleneck, could provide estimates of the intensity of the selection pressure required to stabilize genotypes predisposing to salt sensitivity, which could be compared with evidence from the historic and genomic records. Whether or not these types of analyses support the slavery hypothesis or not, they may help us understand the genetic basis of salt sensitivity.

Evolution, Growth and Development, and Blood Pressure

Ontogeny describes how changes arising from development and ageing impact phenotypes. Blood pressure generally rises throughout life, so understanding ontogeny is part of understanding hypertension. Some developmental changes (eg, the rise in blood pressure during childhood and the acceleration of the rate of blood pressure rise after the adolescent growth spurt) seem biologically preprogrammed, because they are observed even in non-Westernized individuals, whereas others (eg, the inexorable rise of systolic blood pressure throughout adulthood in Westernized societies) are more closely associated with the environment.[34] Can evolutionary theory help to explain age-dependent changes in blood pressure regulation and the development of hypertension?

The "Thrifty Phenotype"

Ontogeny begins in utero and so can a predisposition to hypertension. In groundbreaking observations, Barker et al[35] described an inverse relationship between birth weight and incidence of adult cardiovascular disease, and he and others subsequently demonstrated equally consistent relationships between low birth weight and the prevalence of traditional cardiovascular risk factors, including hypertension, during adulthood.[36] Why these relationships develop is explained by a feature of pregnancy that at first seems counterintuitive: an evolutionarily based struggle for survival between a mother and her offspring. Trivers[37] was the first to point out that because offspring share only half their chromosomes with their mother, as each strives to maximize its chances of survival and reproduction, mothers and offspring compete for resources. This conflict extends to maternal–fetal interactions where, when calories are limited, the fetus will preferentially allocate resources to placental growth to extract as much nutrition as possible from the mother, although that effort comes at the cost of decreased fetal somatic growth. Mothers pursue their own strategies to withhold sustenance from their fetus for their own benefit. Hales and Barker[38] explained that this conflict results in an in utero programming that allows the fetus to anticipate the environment that it will encounter at birth. When that environment is one of scarcity, fetal programming is appropriate and gives the newborn an advantage for survival and reproduction. When a fetus programmed for scarcity is born into an environment of excess, the program is inappropriate and leads to development of the metabolic syndrome. By analogy, with the thrifty genotype hypothesis, Hales and Barker[38] dubbed the "thrifty phenotype" hypothesis, emphasizing the plasticity of the fetal genome in responding to its prenatal environment.

The effects of intrauterine programming are probably numerous,[39,40] but the one most closely associated with a predisposition to hypertension via pressure–natriuresis is the effect of fetal growth retardation on glomerular number and filtration surface.[40] Although direct studies of glomerular morphology are obviously of limited scope in humans, small infants do appear to have fewer, smaller glomeruli, and animal experiments confirm an association of fetal growth retardation and fewer glomeruli.[41] A low glomerular filtration capacity could be the renal lesion requiring the pressure–natriuresis mechanism to operate in a higher blood pressure range.

The intrauterine programming theory of Barker et al[42] predicts some of the postnatal development features of low birth weight infants, including rapid growth during their early years. He recently reported just such a developmental pattern in children, although, interestingly, growth acceleration did not commence until the low birth weight children were 2 years old. An even more important prediction is that good maternal nutrition (as well as attention to the other factors that decrease birth weight) could prevent or delay the onset of some fraction of hypertension. This testable prediction of evolutionary theory could expand our currently meager repertoire of interventions for preventing hypertension.[43]

Allometry and Renal Growth

Obesity is the most important postnatal influence on blood pressure, but other development features of youth may also contribute to a predisposition to hypertension.[44,45] We have suggested previously that hypertension may result from an interaction between the modern environment and the normal allometric coordination of renal and somatic growth.[34] Allometry is the study of the relationships between body size and its components (eg, organ size) and functions (eg, metabolic rate). Allometric equations describing these relationships hold true across a wide range of body sizes within and between species. In particular, kidneys scale to body size with an allometric constant of ≈0.8; that is, renal size is exponentially related to body growth [kidney weight is proportional to (body weight)$^{0.8}$]; in contrast, blood volume scales to body size with an exponent of 1.0. Thus, as bodies grow, absolute renal size always lags behind blood volume, creating a physiological mismatch, and, as our bountiful environment pushes somatic growth to near its genetic limits, a renal functional deficit develops and progresses. In addition, rapid growth is associated with earlier menarche and andarche. Kidney growth essentially ceases at sexual maturity, but body growth continues through the subsequent adolescent growth spurt, further aggravating the mismatch.[34] This physiological mismatch must be compensated, and increasing the set point of pressure–natriuresis is a simple and effective way of normalizing plasma volume.

The hypothesis predicts that the absolute size of a kidney or its components, that is, glomeruli or tubules, will be smaller than the allometric prediction in hypertensive subjects and close to the allometric prediction in normotensive subjects. Furthermore, age at puberty and the pace of growth trajectories in youth and adolescence should correlate with blood pressure later in life. Finally, stature should relate to blood pressure. This last prediction has not been tested but gained some indirect support from an analysis of height and cardiovascular disease: short may be good when it comes to avoiding heart attacks.[46] The possibility of synergies between the effects of intrauterine growth programming and allometric constraints on growth is apparent.

Telomere Attrition

Systolic and pulse pressures rise with age, largely as the result of vascular stiffening. At a cellular level, one measure of age is telomere length. Telomeres are repeated sequences capping the ends of chromosomes that protect adjacent subtelomeric DNA from damage and prevent terminal chromatids from associating during meiosis. Telomeres shorten during each cell replication, and unless restored by telomerase, telomere length eventually becomes limiting, and cells die. Aviv[47] distinguished chronological and biological age by differences in telomere length: shorter telomeres correspond with great biological age regardless of birth anniversary. Jeanclos et al[48] showed that telomere length in circulating cells is a surrogate for vascular age and is, thus, related to pulse pressure. Furthermore, Aviv[49] proposed that increased levels of reactive oxygen species, a feature of our interaction with the novel environment, accelerate telomere attrition and, thus, vascular aging: his theory predicts a relationship between telomere length and oxidative stress. Finally, telomere differences are apparent in utero,[50] and racial differences in the rate of telomere shortening may contribute to differences in the rate of renal growth or glomerular number, which, as noted above, may be an important factor predisposing to hypertension.[51,52]

As is clear from these examples, ontogeny has much to offer to the evolutionary analyses of hypertension. Note that the biological processes discussed, including maternal–fetal conflict, intrauterine programming, allometry, and telomere dynamics, are all controlled by genetic programs, but none of the proposed explanations is deterministic: the same genes do not cause hypertension absent environmental triggers. Each hypothesis leads to testable, specific predictions about how gene–environment interactions predispose to hypertension. In addition, the evolution of development, or phenogenetics, is a currently active area of research that has not yet been extensively applied to the study of human cardiovascular disease.[53] An appreciation of how evolution shaped mechanisms controlling physiology will undoubtedly deepen our understanding of how genes are translated into phenotypes, including those of emergent properties, such as hypertension.

What Are the Phylogenetic Lessons?

Phylogeny is the final necessary component of biological explanation. Phylogenetic relationships describe how taxonomic groups descended with modification from their common ancestors.[54] Because our ancestors survived, at least some of their phenotypic characteristics were adaptations that improved fitness, but those same adaptations now constrain what we can do when faced with new environmental challenges. Phylogenetic constraints are often so obvious that we do not even consider that there could be alternatives. Any engineer could design a spine not susceptible to low back pain, but nature cannot, because the structure of the human spine is a product of our phylogeny. Biological structures are plastic, but only within limits, so some apparent maladaptations are inevitable. As emphasized above, these apparent "flaws" may prove to be adaptive mechanisms rendered deleterious by the modern environment.

The Uric Acid Hypothesis

Watanabe et al[55] have vigorously championed a pathogenetic role for uric acid in hypertension based in part on phylogenetic considerations. Uric acid levels in humans are higher than those of most other mammals (excepting, apparently, guinea pigs and Dalmatian dogs) because we lack the major metabolic pathway of uric acid, hepatic uricase. Johnson et al[56] initially hypothesized that high levels of uric acid could help to maintain blood pressure via vasoconstriction in low sodium environments but that, in modern high-sodium societies, high uric acid may cause subtle renal injury, induce chronic salt sensitivity, and lead to hypertension.

Whether uric acid has a pathogenetic role in hypertension can be questioned,[57] but a selective advantage for uric acid based on the antioxidant properties of uric acid[58] or its role in the immune response[59] has been proposed. If natural selection favored loss of uricase and the attendant development of hyperuricemia, hypertension may be an example of antago-

nistic pleiotropy in the novel environment.[60] Whether inactivating mutations of uricase are the result of selection can be examined formally by the genomic methods discussed above.

Perspectives

Evolution explains how we came to be what we are today, including why we are susceptible to hypertension. Evolutionary medicine has been sorely neglected in the medical curriculum, as well as in most cardiovascular research.[1] In this review, I have attempted to demonstrate the usefulness of an evolutionary analysis of hypertension and to suggest some of the routes by which modern human genomic research will provide information and tools that will extend evolutionary hypothesis testing beyond that possible by phenotypic observations alone. By integrating "why" and "how," I hope we will finally have a chance to address the most important of the "how" questions: how to prevent hypertension.

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