

**Essential Hypertension and Its Causes: Neural and Non-Neural Mechanisms**, by Paul Korner.  
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The word "essential" in essential hypertension (EH) means high blood pressure (BP) of unknown cause, and this is how EH is still widely regarded. This may be due to the multifactorial nature of EH and to uncertainty about the role of the kidney. Some 40 years ago Arthur Guyton suggested that every type of high BP began as volume overload arising from an inability of a dysfunctional kidney to excrete salt. This certainly does not apply to EH in which blood volume is low and the kidney is the victim rather than the source of the high BP. Guyton thought the autonomic nervous system played no role in long-term regulation of BP, but we now know that sympathetic neural activity (SNA) is raised in EH. Clearly, a fresh synthesis of the vast amount of available information on EH has long been overdue.

This became clear when examining the nature of the circulatory control system itself. Most cardiovascular physiologists still regard this as a linear feedback system with fixed parameters and set point. However, it resembles in fact a non-linear man-made "adaptive" control system, in which parameters are actively altered when the operating conditions exceed certain limits. Such parameter changes can occur either acutely, as in haemorrhage during transition from the non-hypotensive to the hypotensive phase, or chronically, as in regular exercise training or in chronic mental stress.

### BP Genetics

We now know from many biometrical studies that genes and environment are both crucial in the development of EH. In contrast, in the Japanese spontaneously hypertensive rat (SHR) the genetic influence is stronger and hypertension develops in almost every environment. The borderline hypertensive rat (BHR, i.e. the F<sub>1</sub> hybrid of SHR×WKY), with half the high BP genes of SHR, provides a better animal model that simulates what happens in EH: their blood pressure (BP) only rises in the presence of environmental reinforcement by chronic stress or a high salt intake.

Unfortunately to date none of the high BP genes have been definitively identified in either EH or SHR. However we know at least that there is a strong probability that some trait differences are genetically determined. Human subjects with a family history of EH respond more strongly to stress tests than those without such a history. In inbred animals there is a strong likelihood for a genetic basis for a trait difference between, for example, SHR and normotensive WKY, if it cosegregates with BP in F<sub>2</sub> or backcross populations. This has been demonstrated for resting SNA, for SNA responses to acute stress and for several other traits. It suggests that failure to identify the underlying genes in EH and animal models of neurally initiated hypertension may be due to neglect of the brain by those working on the field.

### Environmental Causes and Output Patterns as EH Becomes More Severe

We know from various case control and intervention studies, that the main environmental causes initiating EH are mental stress, a high salt intake and obesity. The early rise in BP is largely due to elevation of SNA in the outflows to the heart, renal, gastrointestinal, skin and skeletal muscle beds, with the secretion of adrenaline tending to mask the skeletal muscle vasoconstriction. This is the defence pattern of autonomic activity which arises from specific hypothalamic neuron groups. Non-neural enhancement of vasoconstrictor tone is initially through cortisol-induced reduction in regional nitric oxide (NO), which accentuates the effects of the raised SNA. Later structural changes develop in the large resistance vessels and enhance the overall functional constrictor effects, raising BP further. The vasoconstriction also results in deterioration of the downstream microcirculation, which is known as rarefaction. Eventually the function of kidney, brain and heart become impaired.

The above peripheral changes and the stiffening of the conduit arteries make substantial demands on the heart's pump performance. This is provided by increased inotropic support, development of left ventricular hypertrophy and an adequate coronary blood flow. Eventually an inability to match the peripheral changes produces cardiac failure.

### Brain Mechanisms

All major autonomic effector responses are mediated through neurons that release fast (rapidly acting) transmitters, e.g. glutamate. Other interneurons that carry information from one neuron population to another, release slow transmitters, including monoamines and various peptides. Each slow transmitter modulates the responsiveness of the fast transmitter pathways. For example, in EH (and SHR), repeated increase in dopamine (DA) neuron activity strengthens synaptic transmission of the hypothalamic defence pathway and lowers the threshold for eliciting the sympatho-adrenal changes, which is termed sensitization and is a relatively irreversible process.

*Baroreflexes* contribute to virtually all aspects of circulatory control. In the intact organism the responses depend on the combined changes in arterial, cardiac and pulmonary baroreceptor activity. In every type of hypertension there is a chronic increase in cardiopulmonary load, which gives rise to the well-known vagal deficit, which is evoked through serotonergic neurons stimulated by an increase in activity from medium-high threshold baroreceptors. The vagal deficit disappears rapidly when volume load is reduced.

*Exercise* is a physiological variant of the defence response and is associated with elevation of BP and enhancement of constrictor baroreflexes. Its regulatory drive arises from cortical "command" neurons and from

muscle chemoreceptors, both of which interact with the baroreflex pathways. The cerebellum compares actual to desired skeletal muscle performance and adjusts both muscle performance and SNA in the light of this comparison. It may also be responsible for the transient depression of constrictor baroreflex properties between regular training sessions, that is one factor mediating the anti-hypertensive effect of exercise.

### The Main Syndromes of EH

There are two syndromes: 1) stress-and-salt related EH (SSR-EH), and 2) hypertensive obesity. Both are initiated by psychosocial stress, with the hypothalamic defence response the basis for the initial elevation of BP.

Stress is perceived through the thalamo-cortical system and its intensity is evaluated by the prefrontal cortex. Activity of DA neurons that link the latter to the hypothalamus is responsible for the chronic elevation of BP and sympatho-adrenal activity. In normal subjects these changes revert to baseline when the stress is over. However, in persons genetically susceptible to EH, sensitization of defence pathway synapses leads to virtually permanent elevation of BP, outlasting the stress. Synaptic sensitization is a normal attribute of thalamocortical and memory neurons, but is most unusual in the autonomic nervous system. It suggests that in persons susceptible to EH mutant developmental genes may give rise to ectopic DA synapses with their properties resembling memory neurons.

The chronic vasoconstriction that follows sensitization of the defence pathway increases BP responsiveness to salt by raising sodium permeability of the blood-brain barrier. This increases the activity of brain ouabain neurons that raise BP and SNA through projections to the defence area. Salt thus adds to the stress-related neural increase in BP, resulting in a combined initial rise in BP of about 20 mm Hg. Nonneural factors account for the subsequent further rise of 20-40 mm Hg. There is considerable individual variation in the magnitude of this latter rise, which may also have a genetic basis.

*Hypertensive obesity* is the second syndrome of EH: it is due to superposition of obesity on SSR-EH and accounts for about 40% of all EH. It is a volume overload hypertension, in which the stress-related vasoconstriction is masked by the dilator action of the raised plasma insulin. Insulin also increases fluid reabsorption by the renal tubules. In lean persons with EH the brain mechanisms regulating energy balance function normally in response to changing levels of leptin and other adiposity peptides. However, in a proportion of persons with the cortex ignores these signals: their excess eating is a response to alleviate stress-related anxiety and leads to obesity. Unfortunately, the effect is only transient and their eating eventually becomes an addiction. Subjects with hypertensive obesity develop distinctive complications, notably non-insulin dependent diabetes mellitus and LV failure.

### Prevention and Treatment

Remarkably, the major benefit of most anti-hypertensive drugs is largely through non-specific lowering of BP. This reduces myogenic tone and widens the diameter of the resistance vessels. The cardiovascular structural changes associated with EH are difficult to reverse, though some drugs appear to bring this about more than others, particularly in younger persons. In contrast to the largely non-specific effects of the drugs, the major non-pharmacological forms of management (exercise and reduction of dietary intake of salt and calories) are relatively specific antagonists of the initial SNA-induced elevation of BP. Hence, if they became part of a persons lifestyle from an early age, EH might be prevented. In established EH, these measures should be used more energetically than at present in conjunction with pharmacotherapy, particularly in the treatment of young and middle aged persons with EH. In at least a proportion of this group it may become possible to wean them off anti-hypertensive drugs.

### Other Topics

Obesity also predisposes to obstructive sleep apnea (OSA), which results in elevation of BP. Some regard OSA as another syndrome of EH, but most consider it to be a secondary form of high BP, which develops as a consequence of the nasopharyngeal obstruction. Other factors contributing to EH, including smoking, alcohol intake and other dietary factors have also been considered briefly.

There is a chapter on the role of the kidney in hypertension. It discusses the interpretation of renal transplantation experiments, which have figured extensively in theories regarding the kidney as the source of hypertension. Renal involvement in EH is more gradual than in renal hypertension, in which SNA is also elevated when there is renal ischaemia.

Lastly, a chapter on the pathogenesis of SHR hypertension emphasises the critical role of elevation in SNA in the development of the high BP.

### Conclusion

The brain is the source of the initial rise in BP, through a variant response to the world around us. The present synthesis suggests that it may be timely to refer to EH from now as *lifestyle-related genetic hypertension*. There is a strong case for employing physiological systems analysis when trying to elucidate the pathogenesis of complex disorders like EH. This will help elucidate how critical system components operate at the molecular level, which will eventually lead to new forms of therapy.