Prenatal Programming of Hypertension
Role of Sympathetic Response to Physical Stress

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The hemodynamic response to physical stress has been studied over the past decade, and it is considered an indicator of cardiovascular risk. The blood pressure response during acute exercise includes participation of the sympathetic nervous system, involving brain centers and peripheral reflexes. The sympathetic nervous system has a critical role in the regulation of blood pressure and in the cause of hypertension. Several reports from human and experimental models proposed that increased sympathetic activity is linked to hypertension and cardiovascular and renal diseases. Currently, there are 2 phase III clinical trials testing mechanical manipulations of the sympathetic nervous system as a treatment for hypertension. The SYMPLICITY HTN-3 Study is evaluating the safety and efficacy of renal denervation as a treatment for hypertension. The XR-1 Verification Study is assessing the safety and efficacy of carotid baroreflex activators in patients with drug-resistant hypertension. These clinical trials are the results of decades of research targeting the involvement of the sympathetic nervous system in the cause of hypertension. However, few studies are investigating the causes of dysfunction in this important regulatory system. What triggers the increases in sympathetic nervous system activity is still unclear.

The effects of adverse environment, such as poor nutrition during early development, were proposed as possible causes linked to the cause of chronic diseases later in life. This paradigm is also known as the developmental origins of diseases. Studies in the field of developmental origins of diseases reported that offspring exposed to reduced protein diet developed increased sympathetic nervous system activity associated with hypertension. These studies have a common factor: the stress to which the offspring were exposed during fetal life. Exposure to stress during development can reset several regulatory mechanisms, including the sympathetic nervous system, resulting in abnormal responses later in life.

The study presented by Mizuno et al in this issue of Hypertension proposes an interesting hypothesis to explain the role of sympathetic response in the development of hypertension in adults born small for gestational age. The authors used a well-accepted method to directly measure the renal sympathetic activity at rest and during physical stress by exploring the exercise pressor reflex. This study was not designed to add any new technique for the exploration of renal sympathetic activity. However, the novelty of this report lays on the approach to explore the involvement of sympathetic nervous system and physical stress in an experimental model of prenatal programming of hypertension.

The results reported by Mizuno et al add more evidence supporting the paradigm that dysfunctional sympathetic nerve activity is linked to hypertension in low-birth-weight individuals. Mizuno et al propose that physical exercise can initiate an exaggerated sympathetic response that could lead to hypertension. Additionally, this study highlights the importance of pursuing further studies in the field of developmental programming of sympathetic nervous system. Even more, these results strongly support the necessity for more methods using chronically instrumented animals to provide a comprehensive examination of the sympathetic nervous system.

Studies in humans have reported increased sympathetic activity associated with increase in blood pressure in subjects who were small for gestational age when exposed to psychological stress. Experimental studies also reported evidence for sympathetic involvement in the development of hypertension in offspring exposed to adverse environment during gestation. The autonomic origin of hypertension has heterogeneous determinants, including alterations in respiratory pattern, plasma osmolality, vascular inflammation, angiotensin II responsiveness, and renal pressure-natriuresis. However, the kidneys always appear tightly linked with the sympathetic overactivity in the cause of programmed hypertension. The hypertension induced by prenatal insults is exacerbated by stress in animal models of prenatal programming, such as gestational exposure to dexamethasone and low-protein diet. Dexamethasone-exposed offspring had lower blood pressure under baseline conditions and greater increase of blood pressure when exposed to restraint or peritoneal amphetamine treatment. Offspring exposed to low-protein diet during gestation also showed greater increases in blood pressure only after a noxious nasal stimuli.

The exposure to early stress during development is linked to many changes in neurotransmitter systems and neuroendocrine functions. Prenatal exposure to stress affects adult brain receptor functions, including monoaminergic and glucocorticoid receptor systems, the turnover of norepinephrine, and dopamine and the serotonergic system. All these changes would lead to the resetting of several...
systems often regulated by feedback circuits during a critical period of development. The regulation of autonomic nervous activity during development depends on the balance between sympathetic and parasympathetic systems. However, these systems are also regulated at this point by the afferent information from the mother and the intrauterine environment. Therefore, any adverse condition from the mother or the intrauterine environment will have a profound influence in the way the autonomic nervous system is set to react later in life. An insult during development will initiate adaptive changes to allow fetal survival but will also modify the setting of several regulatory systems leading to abnormal responses to normal stimuli such as exercise, resulting in exacerbated sustained increases in blood pressure (Figure). This abnormal response would predispose to the development of hypertension triggered by the physical stressor, exercise.

Results like these reported by Mizuno et al open the way for controversial discussions but also highlight the importance of personalized interventional treatment. Nowadays, physical activity is closely associated with wellness and fitness, and it is included in programs to promote healthy lifestyle to prevent chronic diseases. Therefore, deeper assessment of individuals’ health history, including birth weight, should be a requirement before any interventional strategy, such as regular exercise programs.

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References
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