Hypertension, TLR4 activation in brain and cardiac hypertrophy

Jawahar L. Mehta1,2*, Zufeng Ding1,2,3*, Shijie Liu1,2,3, Xianwei Wang1,2, and Magomed Khaidakov1,2

1Central Arkansas Veterans Healthcare System, Little Rock, AR, USA; 2Division of Cardiovascular Medicine, The University of Arkansas for Medical Sciences, Little Rock, AR 72212, USA; and 3Key Laboratory for Biomechanics and Mechanobiology of Ministry of Education, School of Biological Science and Medical Engineering, Beihang University, Beijing 100191, China

This editorial refers to ‘Central blockade of TLR4 improves cardiac function and attenuates myocardial inflammation in angiotensin II-induced hypertension’ by R.B. Dange et al., pp. 17–27, this issue.

Hypertension or high blood pressure is a major cause of morbidity and mortality around the world. Fortunately, drug therapy along with dietary and lifestyle changes can reduce blood pressure and, therefore, the complications of hypertension in most individuals. On the other hand, untreated or uncontrolled hypertension leads to cerebrovascular accidents, myocardial ischaemia, heart failure, and cardiac arrhythmias. Over the years, attempts have been made to understand the pathophysiology of hypertension. While the precise cause of hypertension in most of the patients is not known, there is emerging evidence for neuroendocrine activation and insulin resistance syndrome in hypertension. A connection between brain, especially perturbation within the hypothalamic paraventricular nucleus of the brain, and development of hypertension has been proposed. Brain–heart connection is also beginning to be recognized as a determinant of outcome after myocardial ischaemia. Furthermore, there is evidence for immune system activation in hypertension. Resulting inflammation along with neuroendocrine stimulation, especially the activation of renin–angiotensin system, may well play an important role in the pathogenesis of cardiovascular disease in patients with hypertension.

The innate immune response is the first line of defence against pathogens; this system mainly includes epithelial cells that prevent pathogen entry, professional phagocytes (neutrophils and macrophages), the complement system, and pattern recognition receptors. Toll-like receptors (TLRs) are the main pattern recognition receptors that sense various pathogens, including double-stranded RNA, bacterial coat proteins, heat-shock proteins, and other toxins. In mammals, at least 13 members of the TLR family (TLR 1–13) have been cloned. As a member of the TLR family, TLR4 recognizes lipopolysaccharide, a gram-negative bacterial cell wall component that initiates inflammatory response in mammals. TLR4 is the only known TLR able to activate both MyD88- and TRIF-dependent signalling, which induce genes encoding inflammatory molecules and Type I interferon, respectively. The role of TLRs in the development of hypertension is very diverse; for example, the lack of TLR5 has been associated with hyperphagia, hyperlipidaemia, hypertension, insulin resistance, and increased adiposity. TLR4 activity is associated with the development and progression of cardiovascular disease. Global TLR4 deficiency has been shown to protect mice from developing hypoxia-induced pulmonary hypertension. TLR2 or TLR4 knockout animals have been shown to have low heart rates and relatively high parasympathetic tone.

The current work by Dange et al. is an interesting attempt to separate contributions of central and peripheral components of TLR4 signalling to the establishment of hypertension and cardiac hypertrophy. They administered angiotensin II to the rats that resulted in sustained hypertension. These rats had dramatically increased TLR4 expression in the brain. Furthermore, central blockade of TLR4 with intracerebroventricular delivery of TLR4-specific viral inhibitory peptide inhibitor (VIPER) delayed progression of hypertension and development of cardiac hypertrophy. Importantly, central TLR4 blockade significantly reduced myocardial TLR4, TNF-α, IL-1β, iNOS levels, NF-κB activity, and altered rennin–angiotensin system components in angiotensin II-infused rats. In addition, there was a >35% reduction in circulating norepinephrine levels following TLR4 blockade. The authors speculate that brain TLR4 plays a key role in modulating cardiac structure and function.

The authors of the study need to be complimented for the conduct of this elegant study. This study certainly engenders some interesting topics for future research.

First, although the authors demonstrate the importance of blockade of TLR4 in the brain, non-brain TLR4 present in other tissues may also contribute to the regulation of hypertension and systemic pro-inflammatory response. It seems somewhat counterintuitive that brain-specific application of VIPER virtually abolished angiotensin II-mediated changes in cardiac expression of TNF-α and iNOS, and circulating concentrations of TNF-α and IL-1β. It is well established that angiotensin II stimulates the production of cytokines in the isolated heart.

Second, the observations made in this study draw attention to blood–brain barrier permeability issue concerning VIPER, angiotensin II and...
resulting cross-talk between the distressed heart and brain. Studies on the ability of VIPER to cross blood–brain barrier have not yet been conducted. It is possible that despite the brain-specific route of introduction, VIPER could have escaped into the blood stream and affected TLR4 in other tissues. Of note, angiotensin II has been shown to cause a multifold increase in blood–brain barrier permeability, and this further increases possibility of such scenario.12

Third, whether TLR4 blockade affects cardiac fibrosis which often accompanies cardiac hypertrophy during sustained hypertension was not examined in the present study. In this regard, it is to be noted that angiotensin II is a strong trigger for fibroblasts proliferation.13

Finally, whether the observations of inhibition of cardiac hypertrophy by TLR4 blockade in the brain are specific for angiotensin II-mediated hypertension, or relate to hypertension occurring spontaneously, or induced in response to other mediators, as well cannot be discerned from this study.

Overall, the study by Dange et al.10 advances our understanding of the role of immune activation in the brain of mice with angiotensin II-induced hypertension in the development of cardiac hypertrophy. It appears that TLR4 up-regulation in the hypertensive brain activates sympathetic nervous system and pro-inflammatory and pro-oxidant signals in the heart leading to cardiac hypertrophy. These concepts are summarized in Figure 1.

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References