Role of Aldosterone in the Pathogenesis of Hypertension

To the Editor:

In Rankinen and colleagues’ report, the strongest genetic linkage in the whole study was found in chromosome 8q21 (Lod 2.36, \(P=0.0005\)) for the effect of exercise training on submaximal exercise systolic blood pressure (BP) response during cycle ergometry at 50 watts. This locus incidentally contains the gene for \(\text{CYP11B2}\) that codes for aldosterone synthase, a key rate-limiting enzyme for the biosynthesis of aldosterone. This is an important finding, albeit limited to the sedentary white population with normal resting BP. The role of aldosterone in the pathogenesis of hypertension is gaining wider recognition with the finding that nearly 1 in 10 hypertensives has inappropriate aldosterone activity that is amenable to treatment. A recent study found a significant association between submaximal exercise systolic BP and the aldosterone-to-renin ratio, a marker of inappropriate aldosterone activity within the hypertensive population. Another related study found a significant relationship between aldosterone synthase polymorphism and inappropriate aldosterone activity, and this relationship appeared to strengthen with age. What, then, is the clinical significance of Rankinen and colleagues’ findings?

Submaximal exercise systolic BP relates to systemic vascular resistance (SVR), which falls during exercise, a reflection of a normal peripheral vasodilatory capacity. Resting BP, even when below the “treatment threshold,” is not an indication for normal SVR. This is because BP is the product of cardiac output and SVR; hence, it is possible to have a raised SVR, the hallmark of the hypertension disease process, without a raised resting BP because of an adaptation in cardiac output. During exercise however, with the rise in cardiac output, a much higher BP is then produced, and in some cases this leads to an “exaggerated” rise in BP if the SVR is raised or if it fails to fall appropriately. Aldosterone is an adverse modulator of the SVR, and one of its potent secretagogous is angiotensin II, which promotes \(\text{CYP11B2}\) genetic transcription, a process that is likely to be influenced by \(\text{CYP11B2}\) genetic variation. It is known that exercise training blunts exercise renin, angiotensin II, and aldosterone secretion in those with the most to gain in terms of improved exercise performance. This would undoubtedly improve the exercise peripheral vasodilatory capacity in such individuals, leading to a reduction in exercise systolic BP. I believe Rankinen and colleagues’ study can be interpreted to suggest that there is a genetic component to SVR and that inappropriate aldosterone activity could be an intermediate phenotype in the pathophysiology of hypertension.

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Response

Dr. Lim presents several good arguments that would explain the associations between exercise, blood pressure, and aldosterone. In fact, Dr. Lim recognizes, just as we did in the paper, that aldosterone synthase is an excellent candidate gene for exercise blood pressure. \(\text{CYP11B2}\) may indeed turn out to be the gene responsible for the submaximal exercise systolic blood pressure (SBP) quantitative trait locus (QTL) on chromosome 8. However, it should be remembered that \(\text{CYP11B2}\) is only one of several genes around the QTL in question, and a linkage signal with one anonymous microsatellite marker does not allow us to specify which gene or genes are involved. We are currently fine mapping the linkage region in chromosome 8, and we hope to be able to verify in the near future whether the \(\text{CYP11B2}\) or some other gene is involved in the regulation of submaximal exercise SBP response to endurance training.

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