Do Leukocytes Have a Role in Hypertension?

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In this issue of Hypertension, Schmid-Schönbein and colleagues investigate the possible role of leukocytes in the pathophysiology of hypertension. The authors measured leukocyte counts and spontaneous leukocyte activation of freshly drawn blood in spontaneously hypertensive rats (SHR) and normotensive Wistar-Kyoto (WKY) rats. Special care was taken to control various factors (source of rats, age, seasonal changes, type of anesthesia) that may influence leukocyte count and function. The total leukocyte count was greater in SHR when compared with WKY rats. Young SHR (4–8 weeks) already showed a 40% higher leukocyte count as controls at a stage when mean blood pressure was near normal values. Spontaneous formation of superoxide anions, as an indicator for leukocyte activation, was more frequent in SHR than WKY rats. Schmid-Schönbein et al speculate that leukocytes contribute to the pathogenesis of vascular changes and subsequent organ injury in hypertension.

Epidemiological studies have shown correlations between an elevated blood leukocyte count and the risk of various cardiovascular diseases such as myocardial infarction and stroke. Leukocyte count has also been shown to correlate with the extent of coronary artery disease observed at coronary angiography. Moreover, recent studies have demonstrated that activation of leukocytes occurs more frequently in patients with intermittent claudication, unstable angina pectoris, and acute myocardial infarction and may be associated with the incidence and severity of ventricular arrhythmias in the early phase of myocardial infarction. It is possible that the elevated leukocyte count and activation is not an epiphenomenon but instead that leukocytes play a central role in the pathogenesis of the diseases mentioned above. It has been suggested that leukocytes may play a key role in the development of atherosclerosis. However, little is known about the role of leukocytes in hypertension. Activated leukocytes may contribute to the vascular complications of hypertension by a variety of mechanisms.

First, rheological properties of granulocytes may influence microvascular capillary resistance. Stimulated granulocytes have altered rheological properties with an increased tendency to adhere to vascular endothelium. Adhesion of leukocytes may result in capillary leukostasis and subsequent increased vascular resistance. This altered leukocyte-endothelial interaction may not only be restricted to capillaries but may also occur in large arteries. Increased adherence of monocytes to cerebral endothelium has been demonstrated in stroke-prone SHR.

Second, stimulated granulocytes and monocytes are known to release a variety of vasoactive substances. The respiratory burst results in the formation of oxygen-derived free radicals, which may influence vascular tone either indirectly by inactivating endothelium-derived relaxing factor and reducing the release of prostacyclin or directly by contracting smooth muscles. Arachidonic acid metabolites of stimulated leukocytes consist of the potent vasoconstrictor substances thromboxane A2, prostaglandin E2 (as shown for large monkey arteries), and peptidoleukotrienes. Leukocyte-derived thromboxane A2 appears to contribute to pulmonary hypertension in sheep and may account for the increase in coronary resistance with subsequent decrease in myocardial contractility in response to complement activation. Recently, rabbit and human leukocytes have been demonstrated to release a stable vasoconstrictor factor, which appears not to be a cyclooxygenase or lipoxygenase metabolite of arachidonic acid. Thus, stimulated leukocytes may increase vascular tone and subsequently decrease organ perfusion by the release of one or more factors. In addition, cathepsin G, a neutral protease released by stimulated granulocytes, has been reported to generate the potent vasoconstrictor angiotensin II by two pathways. One pathway involves the activation of prorenin to renin; the other cleaves angiotensin II directly from angiotensinogen or angiotensin I. This granulocyte-angiotensin system may also modulate vascular tone.

Third, stimulated leukocytes may initiate platelet aggregation. This process may involve eicosanoids, platelet-activating factor, oxygen-derived free radicals, and other substances released by leukocyte degranulation. Moreover, leukocyte-derived free radicals and proteases may damage vascular integrity.
and endothelial cell function, resulting in potentiation of platelet aggregation. In turn, aggregating platelets release the potent vasoconstrictors serotonin and thromboxane A2, which may produce microvascular obstruction by thrombus formation.

Vascular reactivity in several animal models of hypertension is abnormal. Abnormal vascular reactivity may aggravate direct or indirect vascular effects of stimulated leukocytes. Endothelium-dependent relaxation to acetylcholine is reduced or even abolished in various models of hypertension. In SHR, the impaired vasodilator response to acetylcholine could be increased toward normal by inhibition of cyclooxygenase but not with inhibition of thromboxane A2 synthesis. These results suggest that the endothelium from SHR releases a cyclooxygenase-dependent vasoconstrictor that interferes with acetylcholine-induced relaxation. It has been suggested that prostaglandin H2 is a candidate for this endothelium-derived constrictor factor in SHR. Recently, an impairment of acetylcholine-induced increase in forearm blood flow has also been demonstrated in hypertensive patients.

Leukocyte properties are altered in hypertension. The number of glucocorticoid receptors of mononuclear cells appears to be decreased in SHR. In leukocytes from hypertensive patients, the intracellular pH is more alkaline secondary to an increased Na+-H+ antiporter activity. In addition, an increased Na+ content was found in leukocytes from hypertensive patients and experimental animals, perhaps secondary to an inhibition of the Na+-K+ pump. Whether these findings are relevant to the pathogenesis of hypertension is unclear.

Recently, it has been suggested that immune mechanisms may play a role in the development of some forms of hypertension. A single injection of interleukin-2 given to young SHR has been reported to prevent the development of hypertension. However, this finding could not be confirmed by others.

Chronic immunosuppressive therapy has also been found to partially reduce blood pressure in SHR. Further research, however, is necessary to clarify the nature of this immunologic dysfunction in SHR.

The results presented by Schmid-Schönbein and colleagues support the hypothesis that leukocytes have a role in hypertension. Their findings provide an initial step in the understanding of leukocyte-induced complications in SHR. Further work is necessary in this new exciting area to elucidate the mechanism by which leukocytes contribute to the pathogenesis of hypertension.

References


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