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Editorial

The participation of immunity in the pathogenesis of arterial hypertension☆

La participación de la inmunidad en la patogenia de la hypertension arterial

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Studies conducted to demonstrate the participation of the immune system in the pathogenesis of hypertension are relatively recent. The association of high blood pressure with kidney disease was reported in 1879[1] and the first descriptions of autoimmunity as a generator for these morbid conditions appeared in 1904 when the description of auto-antibodies causing haemolytic anaemia in paroxysmal cold haemoglobinuria[2] ended the reigning hypothesis by Paul Erlich that the body did not harm itself (*horror autotoxicus*).[3]

Pioneering observations on the participation of the thymus in experimental models of hypertension began to appear towards the end of the last century,[4] but it has been during the most recent decades that a growing number of studies[5] were conducted to unequivocally establish the critical role of autoimmunity in the complex aetiopathogenetic mechanism resulting in high blood pressure.[6–8]

Inflammation as a manifestation of immune reactivity in hypertension

It is well established that inflammation at the levels of the kidney, artery wall, and the central nervous system promotes and increases the severity of hypertension. The prohypertensive potential of inflammation in these target organs has been demonstrated in studies in which inflammation was reduced with a variety of immunosuppressant treatments which prevented or improved hypertension in practically all hypertensive strains of rats and mice. Furthermore, experimental induction of kidney inflammation is associated with increased blood pressure.[7]

Kidney inflammation induces hypertension as a result of reducing pressure-natriuresis, which is the adaptive renal

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response to a positive sodium balance.[9] Reducing the natriuretic response mediated by increased renal perfusion pressure, which is caused by tubulointerstitial inflammation, results in oxidative stress with reduced nitric oxide, increases angiotensin activity, and has a profibrotic effects with a loss of peritubular capillars. In the arterial wall, inflammation locally increases the generation of oxygen-reactive species, increases vasoconstrictor tone, and suppresses the endothelial dependent vasodilation. In the central nervous system, inflammation in areas near the third ventricle promotes lymphocyte migration to the arterial wall (which causes vascular inflammation) and stimulates sympathetic nervous system activity which not only increases vasoconstrictor tone, cardiac output, and tubular sodium reabsorption, but also induces stimulation of various features of the immune system.[7]

The participation of lymphocytes in the pathogenesis of arterial hypertension

The role of lymphocytes in the pathogenesis of hypertension was initially observed in pioneering experiments by Svendsen,[4] who demonstrated that nude (athymic) mice did not develop salt-dependent hypertension in the DOCA (deoxycorticosterone)-salt model. The development of hypertension in this experimental model phase was recovered by administration of lymphocytes. The role of T and B lymphocytes in the pathogenesis of hypertension was definitely demonstrated in rats with genetic deficiencies of lymphocyte. Guzik et al.[10] demonstrated that angiotensin II-induced hypertension was suppressed in Rag 1 -/- rats missing lymphocytes, and that the angiotensin response was restored by an adoptive T lymphocyte transfer. Similarly, resistance to hypertension was demonstrated in Dahl rates with no Rag 1.[11] The role of B lymphocytes was demonstrated by Chan et al.,[12] who used BAFFR -/- rats (deficient in B *cell activation factor-receptor*).

Innate immunity, acquired immunity, and autoimmunity in arterial hypertension

Innate immunity, acquired immunity, and autoimmunity play an important role in hypertension. There is evidence of NLRP3 inflammasome activation in salt-induced hypertension[13] and in other experimental hypertension models. In hypertensive patients, it has been shown evidence on the activation of innate immunity, including increases in *toll-like* receptors (TLR) 2 and 4 in peripheral blood monocytes[14] as well as elevation in plasma levels of IL-1Beta and IL-18.[15,16]

All aspects of acquired immunity activation have been demonstrated in experimental models of hypertension, including antigens incorporated into antigen-presenting cells *in situ* and in circulation,[17] and T cell co-stimulation[18] and generation from immune memory.[19] In patients with essential hypertension, there are circulating antibodies targeted at potential pathogenic antigens.[20,21]

Immune system activation may be due to mechanisms dependent on an increase in sodium and auto-antigen generation. Although the hypertensive patient does not have hypernatraemia, increases in the sodium concentration within a range which does not exceed physiological levels are capable of polarising undifferentiated T cells towards generating IL-17 cells by activating SGK1 *(serum and glucocorticoid regulated kinase 1)*.[22,23] IL-17 generation promotes autoimmunity, inflammation, and upregulation of the Na-K-2Cl (NKCC1) co-transporter.[24] The importance of IL-17 generation due to increases in the sodium concentration should be considered in the context of mild chronic increases in serum sodium concentration (≥3 mMol/L) which stimulate the central nervous system and increase blood pressure.[25] Moreover, sodium overloads cause high concentrations of sodium in the subcutaneous tissue bound to glycosaminoglycans. This increase in tissue sodium, with no systemic repercussion, induces TonEBP *(tonicity-responsive enhancer binding protein)* stimulation which increases macrophage infiltration with VEGF-C *(vascular endothelial growth factor-C)* generation and increases the subcutaneous lymphatic network.[26] Under these conditions, the subcutaneous sodium levels may be within the range which could promote the generation of IL-17.[22,23]

Auto-antigens, based on evidence from experimental studies are now being evaluated in humans, these are proteins modified by the generation of isoketals which are the result of lipid peroxidation[17] and heat shock protein 70 (HSP70) family of stress proteins.[27] Participation of the latter may be induced by overexpression and mobilisation to the extracellular space, or by performing its functions of protection and antigen transport to the major histocompatibility complex of the cells presenting the antigen.[28]

A look to the future

The possibility of suppressing or preventing elements that trigger immune reactivity with the aim of preventing or treating hypertension is subject to identifying factors which are surely many and variable in different populations, in different age groups, and in both sexes. Evaluating potential antigens and their pathophysiological generation occupies a good portion of current research on the immunopathogenesis of hypertension and promises results in the not-too-distant future. Furthermore, the possibility that an immunosuppressant treatment could be a valid therapeutic option in severe, treatment-resistant hypertension should be explored. Several studies have demonstrated high levels of circulating cytokines in hypertensive patients, and recently, Chen et al.[29] evaluated a considerable number of patients with kidney disease who had resistant hypertension and found a significant increase in TNFα and IL-6 and reduced levels of TGFβ. In studies with 6–7 years of follow-up, these patients had an increased in mortality and in the incidence of cardiovascular diseases. As was reported in a recent editorial,[30] these results open up the possibility of using anti-IL-6 or anti-TNFα treatments in patients with severe, resistant hypertension. There is an anecdotal report of a short course of treatment with microphenolate mofetil which resulted in transforming a patient's severe, resistant hypertension to an easily controlled hypertension.[31] In-depth studies are needed which can clarify the clinical characteristics and cytokine values which make it possible to predict a potential beneficial outcome of temporary immunosuppression in essential hypertension.

Conflict of interest

None.

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