An impaired neuroimmune pathway promotes the development of hypertension in systemic lupus erythematosus

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Mathis KW. An impaired neuroimmune pathway promotes the development of hypertension in systemic lupus erythematosus. Am J Physiol Regul Integr Comp Physiol 309: R1074 –R1077, 2015. First published June 17, 2015; doi:10.1152/ajpregu.00143.2015.—Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disorder that affects nearly 2 million people in the United States. The majority of SLE cases occur in women at an age in which the prevalence of hypertension and cardiovascular disease is typically low. However, women with SLE have a high prevalence of hypertension for reasons that remain unclear. Because immune cells and chronic inflammation have been implicated in the pathogenesis of both hypertension and SLE and because inflammation has been shown to be regulated by the autonomic nervous system, studies investigating neuroimmune mechanisms of hypertension could have direct and significant clinical implications. The purpose of this review is to introduce a recently described neuroimmune pathway and discuss its potential importance in the development of hypertension and renal injury during SLE.

cholinergic anti-inflammatory pathway; autoimmunity; systemic lupus erythematosus; autonomic dysfunction; blood pressure

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is a chronic autoimmune disorder characterized by aberrant immune function, including increased T cell activation and coactivation of B cells, increased T-helper cell numbers, and decreased T regulatory cells (17, 32). This abnormal T cell activity leads to the increased release of proinflammatory cytokines and differentiation of B cells into plasma cells (6, 17, 32, 37). Consequently, there is increased production of auto-antibodies [e.g., anti-double-stranded (ds) DNA autoantibodies] that form immune complexes, deposit into tissues, and initiate an inflammatory response (42). The resultant increase in inflammation can cause tissue damage in any organ system; however, the kidneys are prominently affected in the form of immune complex glomerulonephritis (4, 42, 44). Of the SLE patients that undergo renal biopsy, nearly all have evidence of a renal abnormality (e.g., glomerulonephritis), and ~50% of these patients have impaired renal function (3, 12). Both of these can promote impaired renal hemodynamics and lead to increases in blood pressure. Indeed, the prevalence of hypertension in patients with SLE reaches as high as 74%, which contrasts sharply with normal healthy women (age ≤ 40 years), where the prevalence is typically only 2.7–14% (4, 40, 42). Despite the prevalent hypertension during SLE, the mechanisms responsible have not been elucidated.

Our laboratory is interested in determining mechanisms that may lead to the development of hypertension during SLE. In our studies, we utilize the female NZBWF1 mouse, an established model of SLE that results from mixing the genetic background of New Zealand White and New Zealand Black mice (2). We and others have demonstrated that these mice produce the anti-double-stranded (ds) DNA autoantibodies characteristic of human SLE (27). SLE mice also have increased number of splenic lymphocytes and impaired renal hemodynamics, and they exhibit renal damage in the form of albuminuria, glomerulosclerosis, and glomerulonephritis (27, 49). Most importantly, the SLE mouse is hypertensive (24–27). Because the SLE mouse has several characteristics similar to human SLE, it is an ideal model to examine the mechanisms that promote hypertension during chronic inflammatory disease.

Mechanisms Involved in the Pathogenesis of Hypertension

Hypertension, a major risk factor for cardiovascular disease, affects one out of every three adults in the United States, and the prevalence of hypertension is expected to increase by 7.2% by the year 2030 (11). The causative factor(s) in most cases of hypertension is unknown, and there is a large population of patients that are resistant to currently available hypertensive therapies. Therefore, there must be a continued effort to investigate mechanisms that may promote chronic elevations in blood pressure to reveal effective and novel therapeutic targets.
Vascular and neural mechanisms have been implicated in the pathogenesis of hypertension, and many studies focus on how these mechanisms cause alterations in the kidneys and contribute to chronic changes in blood pressure. The role of the nervous system, specifically the autonomic nervous system, is intriguing because when there is imbalance between the sympathetic and parasympathetic nervous systems, hypertension may result (36). For example, enhanced sympathetic nervous system activity, specifically through the renal sympathetic nerves, promotes chronic elevations in blood pressure both experimentally and clinically (15, 41). Conversely, reduced parasympathetic nerve activity may also promote hypertension, and there is evidence that alternative medical therapies, such as meditation and acupuncture, which both increase parasympathetic nervous system activity, may protect from chronic increases in blood pressure (19, 34). However, the mechanisms involved are unknown.

More recently, immune dysfunction and inflammation have been associated with the development of hypertension. Immunosuppressive therapy, thought to reduce both T and B cells, attenuates blood pressure in hypertensive patients with underlying rheumatoid arthritis and psoriasis (14). Similarly, animals that lack T and/or B cells are protected from experimental models of hypertension (7, 13). Because immune cells and chronic inflammation may be important in the pathogenesis of hypertension, it is important to understand regulation of the immune response during the disease. It is thought that the autonomic nervous system may control immune responses based on evidence that receptors for neurotransmitters are present on immune cells and also based on the idea that immune cells can themselves produce and secrete neurotransmitters (10). Neural regulation of the immune system may be an alternative way by which the autonomic nervous system can impact renal function and ultimately blood pressure.

Cholinergic Anti-Inflammatory Pathway

The classic inflammatory reflex is an interface between the brain and the immune system that provides a mechanism for neural inhibition of inflammation (35, 45). The afferent arm of the inflammatory reflex is activated by an unbalanced cytokine response from inflamed tissues. The normal efferent arm of this reflex, termed the cholinergic anti-inflammatory pathway, suppresses cytokine release and reduces inflammation (Fig. 1). In this pathway, once the vagus nerve is stimulated, it activates the splenic nerve that subsequently releases norepinephrine (38). Norepinephrine binds its β-adrenergic receptors on splenic ACh-producing T cells to cause ACh release (39, 47, 50), which, in turn, binds to the alpha 7 subunit of the nicotinic ACh receptor (α7-nAChR) on the same or nearby splenic T cells and macrophages through autocrine and paracrine mechanisms, respectively (35, 47, 51). This inhibits the production of pro-inflammatory cytokines (e.g., TNF-α, IL-17, HMGB1).
and release of proinflammatory mediators like TNF-α, IL-17, and high mobility group box 1 (HMGB1) from the spleen, and ultimately reduces systemic inflammation and tissue injury (47). An impaired cholinergic anti-inflammatory pathway would promote chronic inflammation, and since both SLE and hypertension are associated with chronic inflammation, it is of interest to determine whether this neuroimmune mechanism is critical.

Role of the Cholinergic Anti-Inflammatory Pathway in SLE Hypertension

Autonomic dysfunction is common in SLE patients, and studies reveal impaired parasympathetic (vagal) tone during SLE (18, 22, 30, 43). Reduced vagal tone may suggest impairment of the cholinergic anti-inflammatory pathway, and this has been proposed as a possible mechanism leading to systemic inflammation and tissue injury in chronic autoimmune disorders (20, 21) and sepsis (38), as well as essential hypertension (16) and experimental models of hypertension (1, 9, 21). The cholinergic anti-inflammatory pathway could potentially be compromised at several locations: at the level of the vagus nerve (i.e., autonomic/vagal dysfunction), at the level of the cholinergic receptors (i.e., altered numbers of receptors), or at the level of the immune cells (i.e., over-responsive/overactive immune cells). Since both SLE and hypertension are associated with autonomic dysfunction and increased immune cell activation, we hypothesize that the cholinergic anti-inflammatory pathway is impaired during hypertension in the setting of SLE.

The cholinergic anti-inflammatory pathway requires an active vagus nerve; therefore, decreased vagal nerve activity is consistent with an impaired cholinergic anti-inflammatory pathway. We have collected preliminary data that suggest impaired vagal tone in hypertensive SLE mice (28). Additional unpublished data from our laboratory demonstrate splenic α7-nAChR expression is increased in hypertensive SLE mice (23), which may also indicate an impaired cholinergic anti-inflammatory pathway. Others have shown that the α7-nAChR is reduced in experimental models of hypertension in rats (5, 21); however, we propose that any alteration or unbalanced regulation of the receptor may be critical.

The cholinergic anti-inflammatory pathway may be an important target in hypertension research in future years. Stimulation of this pathway has already been shown to be protective in diseases of chronic inflammation (9, 20, 21, 33, 46, 48), and my unpublished preliminary data indicate that pharmacological stimulation of the cholinergic anti-inflammatory pathway via subcutaneous nicotine (2 mg·kg⁻¹·day⁻¹, 7 days), a nonselective agonist of the α7-nAChR, reduces splenic and renal inflammation and protects from the development of hypertension in SLE mice (29). These findings have been reproduced in other preliminary studies that utilize a selective agonist to stimulate the cholinergic anti-inflammatory pathway at the level of the α7-nAChR.

In summary, the cholinergic anti-inflammatory pathway may be important in the pathogenesis of hypertension during SLE. More studies are needed to determine whether reduced vagal tone and alterations in cholinergic receptors, as well as splenic immune cells, contribute to the development of chronic inflammation via an impaired cholinergic anti-inflammatory pathway and whether this increase in inflammation promotes impaired renal hemodynamics and hypertension during SLE.

Perspectives and Significance

SLE is an autoimmune disease that predominantly affects women in 90% of all cases. There is prevalent autonomic dysfunction, immune dysfunction, and hypertension in SLE; therefore, this disease model could be useful in determining the link between neuroimmune mechanisms and hypertension. The cholinergic anti-inflammatory pathway has been implicated in diseases of chronic inflammation; however, the association between this pathway and SLE has not been adequately explored (8). While manipulation of this pathway is promising in other diseases of chronic inflammation like rheumatoid arthritis, the mechanisms of action remain unclear and are the focus of much debate (31). Studies investigating the role of the cholinergic anti-inflammatory pathway in SLE will aid the understanding of how neuroimmune interactions may promote alterations in renal function and lead to hypertension. This insight can potentially lead to novel therapeutic targets for patients with SLE and essential hypertension.

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AUTHOR CONTRIBUTIONS

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