The Eye of the Needle

Redox Mechanisms of Acupuncture Effects in Hypertension

Leonardo Y. Tanaka, Francisco R.M. Laurindo

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Possible roles of oxidative stress and oxidant sources such as Nox nicotinamide adenine dinucleotide phosphate oxidases in the pathogenesis of human hypertension remain yet inconclusive, despite extensive investigation, while antioxidant clinical trials have been mostly negative.[1] Although Noxes and mitochondrial dysfunction indeed amplify vascular dysfunction and inflammation in hypertension, their precise role in blood pressure (BP) regulation has been hard to pinpoint.[1] This uncertainty reflects the complex mechanisms linking disrupted redox signaling to BP control, making it hard to put together the numerous relevant redox target(s). Meanwhile, an emerging relevant site of redox signaling integration is the central nervous system (CNS).

Central neurogenic processes integrating afferent systemic input signals with efferent autonomic regulation are crucial for disturbed cardiovascular regulation in hypertension. Increased sympathetic nervous activity associates with most forms of hypertension, including essential hypertension.[2] The rostral ventrolateral medulla (RVLM) is the most important node integrating afferent signals from distinct CNS areas into barosensitive efferent signals to preganglionic neurons.[2] Most RVLM neurons are glutamatergic and some adrenergic. A major upstream RVLM connector is the nucleus of the solitary tract, which receives projections from several afferent sensory pathways including baroreceptors, heart mechanoreceptors, and spinal cord, responsive to physical, metabolic, and chemical variables. Enhanced sympathetic outflow via RVLM underlies neurogenic hypertension as a short- or long-term BP regulator.[2] Previous work showed that disrupted redox regulation of the RVLM and interconnected structures underlies neurogenic hypertension. RVLM oxidative stress via mitochondria or Noxes[1] supports neurogenic hypertension secondary to angiotensin-II infusion or in the spontaneously hypertensive rat (SHR).[3] Analogous results were shown for the subfornical organ or the whole AV3V area (the region anterior and ventral to the third ventricle),[3] which are upstream RVLM-connecting circumventricular structures displaying attenuated blood–brain barrier and thus exposed to circulating factors including angiotensin-II or cytokines (Figure). The main hypertension-related RVLM Nox subtype is Nox2, with other subtypes reported in interconnected CNS regions.[1] Oxidative stress is accompanied by inflammation, endoplasmic reticulum stress,[3] and MAPK (mitogen-activated protein kinase) signaling,[4] all relevant to hypertension development. However, despite such evidences supporting a causal role of CNS oxidative stress in hypertension, whether and how redox-dependent overactivation of RVLM sympathetic outflow can be a therapeutic target remained unexplored.

In this issue, a study by Wang et al[5] provides relevant insights into these questions. The authors started from experimental studies reporting acupuncture-mediated decrease in oxidative stress[6] and inflammation[7] in distinct disease conditions, as well as acupuncture-induced BP decrease in patients.[8] They interrogated whether mechanisms underlying such effects involve an integrative redox response at the RVLM. Their results show that acupuncture, applied at specific acupoints but not at nonacupoints, markedly attenuates high BP and sympathetic activation in SHR without affecting wild-type Wistar-Kyoto rats. This protective effect correlated with downregulation of expression and activity of Nox2, but not Nox1 or Nox4, at the RVLM. Such antihypertensive and sympatholytic effects were mimicked by RVLM administration of antioxidants or nonspecific Nox inhibitors, suggesting that oxidative stress plays a causative role in those processes, rather than being a neutral epiphenomenon. Importantly, protective acupuncture effects were negated by locally inducing nicotinamide adenine dinucleotide phosphate oxidase activation with tetrabromocinnamic acid, further supporting that buffering of RVLM Nox-derived oxidants is a mechanism of acupuncture. Microarray experiments and direct validation showed that overactivation of p38 (a MAPK subtype) and ERK1/2 (extracellular signal-regulated kinase 1/2) in the RVLM was decreased by acupuncture, indicating potential direct downstream Nox targets, in line with known crucial roles of RVLM p38 for angiotensin-II pressor effects.[4] Of note, a role for RVLM metabolic reprogramming in acupuncture can be speculated because microarray analysis showed metabolic genes as the top hit. Considering previous reports, the most likely nature of RVLM oxidative stress in the SHR relates to inflammatory mediators, given the known analogous changes observed in neurogenic hypertension mediated by direct angiotensin-II administration.[3] Mechanisms of such inflammation in the SHR probably include direct effects of circulating angiotensin-II or cytokines on circumventricular structures upstream to the RVLM. Oxidative stress may spread from circumventricular structures to the RVLM via

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(*Hypertension*. 2018;71:224-226.
DOI: 10.1161/HYPERTENSIONAHA.117.09821.)

Hypertension is available at http://hyper.ahajournals.org
DOI: 10.1161/HYPERTENSIONAHA.117.09821

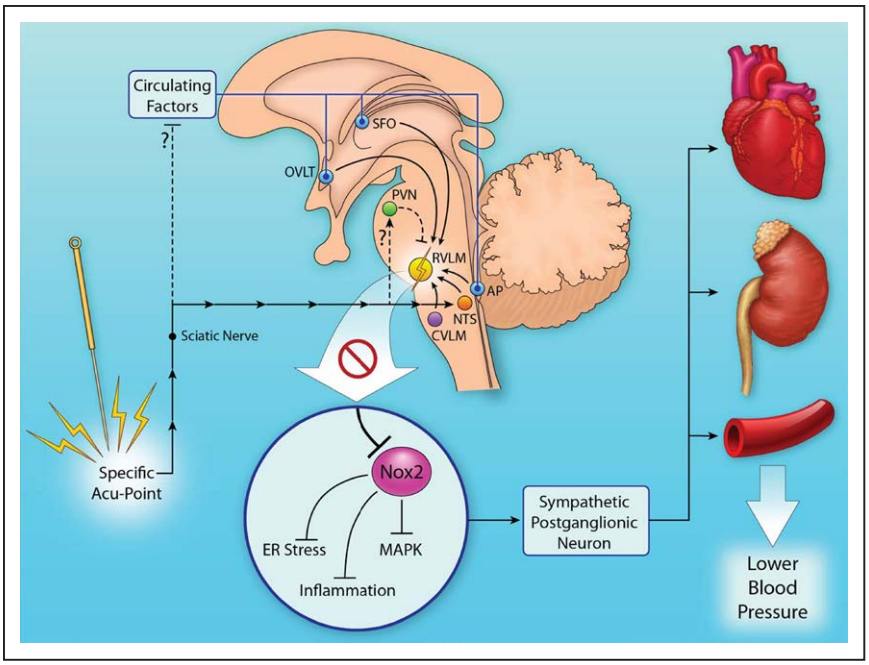

Figure. Scheme depicting possible afferent pathways triggered by acupuncture, with related neural connections to the rostral ventrolateral medulla (RVLM), culminating in decreased Nox2 (nicotinamide adenine dinucleotide phosphate oxidase 2) and MAPK (mitogen-activated protein kinase) activation, leading to decreased sympathetic outflow to target organs. Effects on RVLM inflammation and endoplasmic reticulum (ER) stress, as well as dotted lines depicting circulating factors and connections to the other neural structures were not directly addressed by Wang et al[5] and are derived from published data discussed in the text. Area postrema (AP), organum vasculosum laminae terminalis (OVLT), and subfornical organ (SFO) are circumventricular structures displaying an attenuated blood–brain barrier. CVLM indicates caudal ventrolateral medulla; NTS, nucleus of the solitary tract; and PVN, paraventricular nucleus.

several mechanisms, including direct diffusion of oxidants or inflammatory mediators, secretion of stress-related proteins or oxidant sources, glial activation, and microparticles. Although inflammatory mediators per se exacerbate or disrupt redox signaling, associated processes including autophagy, senescence, apoptosis, and endoplasmic reticulum stress[3] further modulate such redox scenario.

Potentially the major contribution of this study was to show that afferent stimuli to the RVLM can be exploited as a redox-related therapeutic strategy in hypertension (Figure). A corresponding crucial proof-of-concept experiment was the demonstration that sciatic nerve resection or local capsaicin application prevented antihypertensive and sympatholytic effects of acupuncture, as well as diminished RVLM oxidative stress/Nox activity. Similarly, sciatic nerve resection reportedly prevented protective acupuncture effects against neurodegeneration, including Nrf2 (nuclear factor erythroid 2-related factor 2) expression.[6] Nrf2 was a less likely mechanism in the present study,[5] given unaltered superoxide dismutase expression and activity. Proximal mechanisms of acupuncture effects are still unclear, including questions about the precise nature of subcutaneous neural plexuses putatively behaving as acupuncture receptors. Similarly, the routes whereby acupuncture signals transit through the brain stem to reduce sympathetic outflow are unclear but may include endorphinergic opioid mediators from the paraventricular nucleus.[9] Enhanced vagal tone from acupuncture is another important component known to attenuate inflammation after heart ischemia–reperfusion[10] and proinflammatory adrenal dopamine release during sepsis.[7]

As usual, these results raise several questions and caveats. A main point relates to well-known technical limitations of redox research on issues such as interpretation of dihydroethidium fluorescence, specificity of Nox inhibitors/agonists, and Nox activity measurements. Thus, although the body of results by Wang et al[5] has strength, interpretation of specific results may have to be taken carefully. In particular, it remains important to validate such results in transgenic animal models of Nox loss or gain of function. An open question is whether acupuncture-derived signals directly affect RVLM redox/Nox-related processes, as opposed to decrease in inflammation and BP normalization. Another issue is the substantial neurogenic component of hypertension in the SHR, raising questions about whether similar effects would occur in non-neurogenic models of hypertension. In parallel, given the multiple afferent pathways to the RVLM (Figure), it is relevant to investigate the effects of acupuncture in afferent costimuli to the RVLM, including metabolic changes, physical exercise, systemic inflammation, or psychological stress. Because adrenal epinephrine secretion is partly under RVLM control,[2] addressing circulating catecholamine levels in these settings is likely important. Also, although acupuncture did not affect BP and sympathetic activity in normotensive rats, its potential preventive effects can be worth of attention. All these questions will help clarify possible therapeutic roles of acupuncture for human hypertension. Systematic analysis of the available, yet short-scale, clinical studies discloses benefits of acupuncture as an adjunctive therapy, although the effects of isolated acupuncture are still inconclusive.[8]

In summary, the results by Wang et al[5] help illuminate the redox pathophysiology of hypertension, reinforcing the RVLM as a hub of Nox/redox-related events in this condition. Moreover, this study introduced the novel concept of therapeutically manipulating the CNS redox state in hypertension via nonpharmacological afferent stimuli. Ultimately, further investigation on the mechanisms and pattern of such effects may set the stage to justify large-scale clinical trials of acupuncture as a possible novel antioxidant therapy in hypertension.

Sources of Funding

The authors are supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), CEPID-Redoxoma grant 2013/07937-8, and scholarship grant 2013/17115-5 to L.Y. Tanaka.

Disclosures

None.

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Hypertension. 2018;71:224-226; originally published online December 11, 2017;
doi: 10.1161/HYPERTENSIONAHA.117.09821
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563