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INDIAN SOCIETY OF HYPERTENSION

CURRENT MEDICAL CONCEPTS

10.5005/jp-journals-10043-0027

HYPERTENSION AND NEUROGENIC IMPACT

Neurogenic Factors and Blood Pressure Regulation

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ABSTRACT

Over the years, clinical and experimental studies have established the pivotal role of neurogenic factors in the genesis, progression, and prognosis of hypertension. It is accepted that sympathetic nervous system dominance over vagal influence is largely responsible for hypertension. Such an imbalance is seen strikingly in resistant hypertension. Lifestyle modifications leading to reduced sympathetic tone and increased vagal tone consistently provide control of hypertension and to some extent reversal or delaying of end-organ damage. However, studies with pharmacological and device-based therapies that aimed to modify autonomic tone to regulate neurogenic factors and to achieve desired blood pressure control have not produced encouraging results. The role of beta-blocker drugs has also been questioned. Catheter-based renal denervation strategy has fallen short of expectation. Understanding thoroughly the mechanisms underlying alterations in the neurogenic factors, the result of abnormal neurogenic milieu at the cellular and molecular levels and methods to identify susceptible individuals either by genetic study or by accurate measures of autonomic tone is expected to help tailor anti-hypertensive therapy and thereby improve outcomes.

Keywrods: Anti-natriuresis, Glutamatergic synapse, Vasomotor sympathetic nerve discharge.

How to cite this article: Pandurangi UM. Neurogenic Factors and Blood Pressure Regulation. Hypertens J 2016;2(1): 35-38.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Extensive research regarding the pathogenesis of hypertension over last several decades has established that hypertension is the result of highly complex and multifactorial mechanisms.[1] Neurogenic factors have been regarded to exert the maximum influence on not only the pathogenesis of hypertension but also its maintenance, aggravation, and adverse sequelae.[1,2] Tilting of neurogenic environment toward autonomic sympathetic dominance has the potential to promote hypertension by adversely affecting the vascular reactivity, blood vessel elasticity, blood viscosity, circulating blood volume, and cardiac output.[3] Autoimmunity and inflammation favoring hypertension can also be modulated by neurogenic factors.[4] Many of the mechanisms involved in genetic and lifestyle predisposition to hypertension are based on neurogenic factors as effectors. The pathophysiological role of neurogenic factors is discussed and debated in the guidelines. They are not solely because of the lack of evidence for their role. The lack of evidence-based proof-of-significant benefit in the clinical medicine by the therapies to modulate neurogenic factors contribute dominantly to the controversy.[5,6] Current strategy of regulating favorably the neurogenic factors is fraught with adverse hemodynamic, metabolic, and endocrinologic consequences.[5,7] Further understanding of the neural mechanisms governing blood pressure (BP) regulation will yield possible newer and rational drugs to treat hypertension.

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Evidence for Neurogenic Factors in Hypertension

The theory of neurogenic factors regulating BPs received credence as early as in the beginning of 20th century when observations of rise of BP in response to psychoemotional stimuli and control of hypertension by bilateral splanchnicectomy were made.[1,2] The diurnal variation of BP even in normotensive individuals is the result of neurogenic factors exemplified by lower BP level during sleep when there is low sympathetic drive and surge in BP to its overdrive on awakening.[1,2]

The microneurographic studies have shown that the number and amplitude of sympathetic bursts are higher not only in individuals with a family history of hypertension but also in those with white-coat and masked hypertension.[2]

Evidence is strong to prove that sympathetic overdrive is not a mere epiphenomenon and it is imperative in the end-organ damage. Higher levels of sympathetic discharges are seen in patients with left ventricular hypertrophy or dysfunction, renal dysfunction, and other vasculopathies.[3] The histofluorescent and electron microscopic analysis of the sympathetic innervations have revealed that the vessels and the organs in subjects with longstanding hypertension and typically with end-organ damage have a greater density of sympathetic innervations.[2]

Excess sympathetic nerve discharge is noted in young, middle-aged, and elderly hypertensive individuals, in

pregnancy-induced hypertension, and also in hypertension associated with metabolic syndromes. In addition to sympathetic hyperactivity, a concomitant diminished vagal influence is often seen in hypertension.[1,2]

Constant sympathetic discharges peripherally lead to downregulation of adrenergic receptors that may partly offset the consequences of sympathetic hyperactivation. However, central sympathetic tonic discharges and concomitant hypovagal milieu perpetuate adverse neurogenic influence. Indeed, sympathetic activation is normally more pronounced in longstanding and complicated stages of hypertension.[1,2]

Recently, the genetic mechanisms predisposing to increased sympathetic tone and hypertension have received attention.[8] A gene-encoding melanocortin-4 receptor is considered to regulate BP *via* adrenergic mechanisms. Subjects showing a melanocortin-4 receptor deficiency display a reduced adrenergic function coupled with low-BP values. Another gene-encoding phosducin is being implicated. Phosducin plays a role in modulating the adrenergic and BP responses to stress and thus in determining stress-induced hypertension. A specific polymorphism of α-1A-adrenoreceptor gene is associated with hypertensive patients affected by metabolic syndrome.

It is also seen that the putative genetic, environmental, and immunological factors implicated in essential hypertension become effective when neural mechanisms loose equilibrium.[2]

The exact mechanisms that trigger altered neurogenic milieu are unclear. However, what is known clearly is that they do not necessarily reside centrally and they may reside in a peripheral organ and they are governed by "feedback" loop.[1,2]

Neurogenic Axis and the Neurogenic Factors in Blood Pressure Control

The regulatory region of central autonomic nervous system that synthesizes the afferent inputs and sends efferent commands is believed to be situated over a wide area in the mid-brain and medulla.[9] It receives continuous information from the pressure-sensitive nerve endings (baroreceptors) situated in the carotid sinus and aortic arch, chemoreceptors in the carotid body, pulmonary parenchyma, and also inputs from the limbic, cortical, and midbrain structures, which are sensitive to behavioral changes.

Afferent fibers from baroreceptors terminate within the nucleus tractus solitarii (NTS), located in caudal medulla and excite second-order neurons *via* a glutamatergic synapse. The second-order neurons from NTS then reach caudal and rostral ventrolateral medulla (RVLM), which in turn provide tonic excitatory drive to the preganglionic sympathetic neurons in the spinal cord. Stimulation of rostral ventral medulla by glutamate or electrical stimulation produces rise in BP. Such response can be blocked completely by cervical spinal cord transaction and partially by pharmacological blockade of α- and β-adrenoceptor blockers. Microinjection of γ-aminobutyric acid (GABA) into the RVLM produces a marked and dose-dependent reduction of arterial pressure.

Vasomotor sympathetic nerve discharge is also influenced by the paraventricular nucleus of the hypothalamus (PVH) by its connections with lower brainstem and spinal cord. The cells in the anteroventral region of the third ventricle of the hypothalamus (AV3V) are sensitive to plasma concentrations of several hormones related to arterial pressure and body fluid composition. The signals originating from here are transmitted to the PVH.[9]

Nitric oxide produced in the NTS and the RVLM is an inhibitory modulator of central sympathetic outflow by regulating glutamate release. Brain angiotensin II enhances sympathetic outflow by blunting the sensitivity of the baroreflex and stimulates secretion of vasopressin *via* its action at various hypothalamic and medullary areas. These central actions of angiotensin II are mediated by AT_1 receptors. Peripherally, angiotensin II at the nerve endings increases catecholamine release through AT_1 presynaptic mechanisms and decrease presynaptic reuptake. The sympathetic neural influences on BP control are mediated by one or more of the following four efferent limbs: Cardiac postganglionic sympathetic chain, vascular postganglionic sympathetic chain, adrenal medullary release of catecholamines, and activation of renin-angiotensin-aldosterone axis through stimulation of renal juxtaglomerular apparatus. The cardiac postganglionic sympathetic chain discharges regulate rhythm, contractility. The postganglionic vascular sympathetic discharge result in increased vascular tone that is mediated by enhanced calcium influx through voltage-dependent calcium channels. The renal sympathetic nerve activation promotes renin-angiotensin-aldosterone axis. Such activation results in anti-natriuresis *via* reduced renal tubular sodium excretion and increased renovascular resistance.[1,2]

Therapeutic Implications

The benefits of BP lowering treatment are well established. The largest-ever meta-analysis of hypertension treatment trials, which was published recently, included 123 randomized controlled trials (over 600,000 participants) published between 1996 and 2015. Each 10 mm Hg reduction in systolic BP reduced the relative risk of major cardiovascular events by 20% and all-cause mortality by 13%.[10] Lifestyle modification in the form of behavioral

changes to minimize mental stress and anxiety, physical exercise, and weight reduction alter neurogenic factors to achieve reduced sympathetic drive and increased parasympathetic drive.[5] Dietary sodium restriction may aggravate the already present sympathetic activation in certain cases. It may be prudent to not to prescribe low-salt diet to all hypertension patients.[11]

Ironically, usefulness of beta-blocker drugs, which act primarily at sympathetic nervous system in the management of hypertension, has come into question.[6,7] Experts hesitate to consider beta-blockers as the first line of antihypertensive drugs. Several trials and meta-analyses have shown that they are inadequate in preventing coronary events and strokes and also highlighted side effects. Paradoxically, the same experts regard beta-blockers as first choice in patients at a high risk for coronary disease, postmyocardial infarction (MI), or heart failure.[5] The relegation of beta-blockers to inferior position may be result of trial designs, inadequate and nonselective sympathetic blockade, or their combinations.[5-7]

The central sympatholytics such as methyldopa, clonidine, reserpine, and guanethidine and peripheral alfa blockers also have fallen out of favor due to their side effects and inferior outcomes in antihypertensive drug trials.[5] The drugs recommended to treat hypertension either directly or indirectly alter favorably the influence of neurogenic factors.[5] Calcium channel blockers diminish calcium influx into vascular smooth muscle cells by interfering with voltage-dependent calcium channels.[5] These channels are activated by adrenoreceptor stimulation. Angiotensin converter inhibitors and angiotensin receptor inhibitors block renin-angiotensin-aldosterone axis and thus reduce the deleterious effects of sympathetic hyperactivity.[5]

Successful treatment of hypertension however is difficult. The prevalence of resistant hypertension is reported to be ranging from 5 to 20% of cases.[12] It is acknowledged that, for those diagnosed with resistant hypertension, therapeutic options are limited and these patients have a three-fold increase in cardiovascular risk compared with those with controlled hypertension, emphasizing the need for alternative therapeutic options beyond pharmacological strategies.

Selective disruption of sympathetic nerve supply to achieve BP control was hypothesized after the results of wider surgical resection of thoracic, abdominal, and pelvic sympathetic nerves for resistant hypertension were analyzed.[1,2] Even though sustained BP control was achieved, perioperative mortality was high, and long-term deleterious effects including significant dysfunction of organs (bladder, bowel, and genitals) supplied by these nerves were noted. Renal sympathetic nerves, afferent and efferent, which are embodied within the wall of the renal artery and are required for maintenance of hypertension, became an attractive target for selective disruption of sympathetic nerve supply. Percutaneous transcatheter renal artery denervation, first explored in the early 2000s, has become one of the options to treat resistant hypertension.[13] Few trials are underway to determine the optimal ways of achieving denervation.

Electrical stimulation of the carotid sinus baroreflex system, or baroreflex activation therapy, may decrease BP in patients with resistant hypertension. Feasibility studies have shown reductions in BP after implantation of a device designed to stimulate the carotid baroreflex system.[14]

The technique of deep brain stimulation as a therapy for hypertension was hypothesized when its effect of lowering of BP was noted in patients with neuropathic pain. The reduction in BP was attributed to improved baroreflex sensitivity. The target for stimulation is the ventrolateral periaqueductal gray, which influences the autonomic outflow.[15]

CONCLUSION

Research has irrefutably established the pivotal role of neurogenic factors in the regulation of BP. Lack of significant clinical benefit by pharmacological and measures to modulate neurogenic factors has highlighted the need to understand neural mechanisms of hypertensions better. In the wake of increasing burden of hypertension and increasing prevalence of resistant hypertension, a fresh look at the more selective beta-blockers with better antihypertensive profile is recommended. Novel nonpharmacological therapies to modulate the neurogenic factors in the management of hypertension hold promise.

REFERENCES

1. Coffman TM. Under pressure: the search for the essential mechanisms of hypertension. Nat Med 2011 Nov 7;17(11): 1402-1409.
2. Grassi G. Assessment of sympathetic cardiovascular drive in human hypertension: achievements and perspectives. Hypertension 2009 Oct;54(4):690-697.
3. Zukowska Z. Atherosclerosis and angiogenesis: what do nerves have to do with it? Pharmacol Rep 2005;57(Suppl): 229-234.
4. Harrison DG, Guzik TJ, Lob H, Madhur MS, Marvar PJ, Thabet SR, Vinh A, Weyand CM. Inflammation, immunity and hypertension. Hypertension 2011 Feb;57(2):132-140.
5. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults report from the panel members appointed to the eighth Joint National Committee (JNC 8). JAMA 2014 Feb 5;311(5): 507-520.
6. Messerli FH, Bangalore S, Julius S. Risk/benefit assessment of beta-blockers and diuretics precludes their use for

first-line therapy in hypertension. Circulation 2008 May 20;117(20):2706-2715.
7. Beevers DG. The end of beta-blockers for uncomplicated hypertension? Lancet 2005 Oct 29-Nov 4;366(9496):1510-1512.
8. Grassi G. Phosducin: a candidate gene for stress-dependent hypertension. J Clin Invest 2009 Dec;119(12):3515-3518.
9. Ross CA, Ruggiero A, Park DH, Joh TH, Sved AF, Fernandez-Pardal J, Saavedra JM, Reis DJ. Tonic vasomotor control by the rostral ventrolateral medulla: effect of electrical or chemical stimulation of the area containing C1 adrenaline neurons on arterial pressure, heart rate, and plasma catecholamines and vasopressin. J Neurosci 1984 Feb;4(2):474-494.
10. Ettehad D, Emdin C, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2015 Dec 23 [Epub ahead of print].
11. Grassi G, Dell'Oro R, Seravalle G, Foglia G, Trevano FQ, Mancia G. Short- and long-term neuroadrenergic effects of moderate dietary sodium restriction in essential hypertension. Circulation 2002 Oct 8;106(15):1957-1961.
12. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, White A, Cushman WC, White W, Sica D, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation 2008 Jun 24;117(25): e510-e526.
13. Bhat A, Kuang YM, Gan GCH, Burgess D, Denniss AR. Renal denervation for resistant hypertension? An update on renal artery denervation and its clinical impact on hypertensive disease. BioMed Res Int 2015;2015:607079.
14. Heusser K, Tank J, Engeli S, Diedrich A, Menne J, Eckert S, Peters T, Sweep FC, Haller H, Pichlmaier AM, et al. Carotid baroreceptor stimulation, sympathetic activity, baroreflex function, and blood pressure in hypertensive patients. Hypertension 2010 Mar;55(3):619-626.
15. O'Callaghan EL, McBryde FD, Burchell AE, Ratcliffe LE, Nicolae L, Gillbe I, Carr D, Hart EC, Nightingale AK, Patel NK, et al. Deep brain stimulation for the treatment of resistant hypertension. Curr Hypertens Rep 2014 Nov;16(11): 493.