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Review Article

Narrative approaches to treat hypertension: Emerging therapeutic perspectives

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Abstract

Various pathophysiologic facets contribute to the pathogenesis of hypertension and are root causes of cardiovascular diseases with end-organ damage. Seeing that, reninangiotensin pathway along with sympathetic nervous system are predominantly involved in HTN development and recently targeted with conventional antihypertensive therapies including diuretics, b-blockers, and calcium channel blockers, renin–angiotenin–aldosterone system antagonists with erratic results. Although current therapeutic modalities target these contributory factors but still not effectual in the apt management of blood pressure in many populations thus pointing towards the inevitability of newer pharmacological as well as non-pharmacological approaches to not only manage but cure this perplexing disorder. Aldosterone synthase inhibitor, selective aldosterone receptor antagonist, prorenin inhibitor and vasopeptidase inhibitor in company with other complementary alternatives consisting of vaccine based strategies, gene based therapeutics (targeting both vasodilatory genes along with vasoconstrictor genes), fine-tuning of endothelium-mediated responses and device base interventions including baroreflex sensitization and renal sympathetic denervation may lead to more effective , curative or preventive employment against CVS diseases. Hence, these narrative approaches in HTN therapeutics are although slow in progress but intriguing area which in future might be more beneficial in the treatment and management of hypertension in majority of populace with minimum risks.

Keywords: Hypertension, Innovative targets, Renin, Aldosterone, Genetic target

Introduction:

Innovative strategies for the management of hypertension have become mandatory despite of numerous notable advances in the treatment of hypertension (Unger *et al*., 2011).Hypertension is a major public health issue and may be the cause of morbidity and mortality in developing countries (Kaur *et al*., 2011). Although conventional therapeutic approaches are effectual in the control of hypertension but in several masses blood pressure is not properly managed this is because these pharmacological approaches may have reached a plateau in their effectiveness and newer remedies need to be investigated with managed (Katovich *et al*., 2005). The long-established antihypertensive therapies including diuretics, b-blockers, and calcium channel blockers are erratically successful in achieving the exigent blood pressure values in hypertensive patients. Moreover, RAAS (renin–angiotensin–aldosterone system) antagonists, converting enzyme inhibitors, receptor blockers, renin inhibitors, and mineralocorticoid receptor blockers attain a great success in this aspect. Nevertheless, treatment of hypertension is at a standstill, a world-wide problem (Unger *et al*., 2011). So, novelty in antihypertensive therapy is prerequisite and judged on the basis of treating resistant hypertension, approaching for future risk issues, capability to manage blood pressure and to tightly control B.P rather than a specific treatment (Unger *et al*., 2011**).** Before discussing innovative therapeutics, there is a need to understand the physiology of hypertension. Here we mainly discuss the physiology of RAAS, sympathetic nervous system and innovative drug targets in these system. Distinctive approaches in antihypertensive therapy mainly have effects on RAAS and SNS. Distinctive approaches involve gene based therapeutics and vaccine therapeutics (Katovich *et al*., 2005). In this review we will give an overview of novel treatment paradigms and future forthcomings in antihypertensive therapy as shown in (Table 1).

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Different pathophysiologic mechanisms in hypertension:

Hypertension begins with oodles pathophysiologic factors and mainly involves kidney, blood vessels and heart. A general idea of factors to simplify the complex pathophysiologic network of hypertension is given in (Table 2) (Kaur *et al*., 2011).

Table 1: Novel treatment paradigms and future forthcomings in antihypertensive therapy

Novel treatment paradigms	Future forthcoming
Innovative therapeutics targets	Enzyme (cymase,tonin,cathapsin G)
Gene based therapeutics (Transcription modulating drugs)	Dihydropyridine based compounds in aldosterone synthase inhibitor
Vaccine based therapeutics	Vaccine against renin
Advance techniques for controlling B.P	
New inhibitors of enzymes	

Table 2: Pathophysiologic mechanisms of Hypertension

Organ	Pathophysiologic factors	Note
CNS	Sympathetic activation	Possibly by stress, angiotensin II production
Heart (cardiac)	Increased cardiac output	Increased peripheral resistence ,blood volume due to angiotensin II, aldosterone secretion,abnormal adrenergic receptors activity
Kidney (renal)	Sodium retention	Increase rennin activity
Blood Vessels	Abnormalities of resistance vessels	Angiotensin II,a vasoconstrictor production
GIT	Obesity.micronutrients	
Endocrine gland	Insulin,aldosterone	Insulin resistance, aldosterone secretion
Endothelium	Environmental Deficiencies of vasodilators	Stress, Endothelin,nitric oxide, natriuretic peptides

Targeting antihypertensive therapy for lowering blood pressure emphasize on understanding multipart mechanisms of hypertension. In this complexity, renal mechanisms perhaps play a chief role even though several factors clearly throw in to the pathogenesis and maintenance of blood pressure elevation (Lifton *at al*., 2001). Supplementary to this mechanism are sympathetic nervous system activity and vascular remodeling. In addition, increased endothelial derived vasoactive factors and kallikrein– kinin expression are also entailed. Eventually, all these pathways play key role in hypertension development and interact with each other at various stages (Carretero *et al*., 2000).

Physiology of renin angiotensin aldosterone system:

A key element of current approaches to cardiovascular (CV) risk reduction is RAAS reticence that reduces BP pharmacologically and the established simplified RAAS image has lately bowed to a complex network as depicted in (Figure 1, 2 & 3) (Foëx & Sear, 2004).

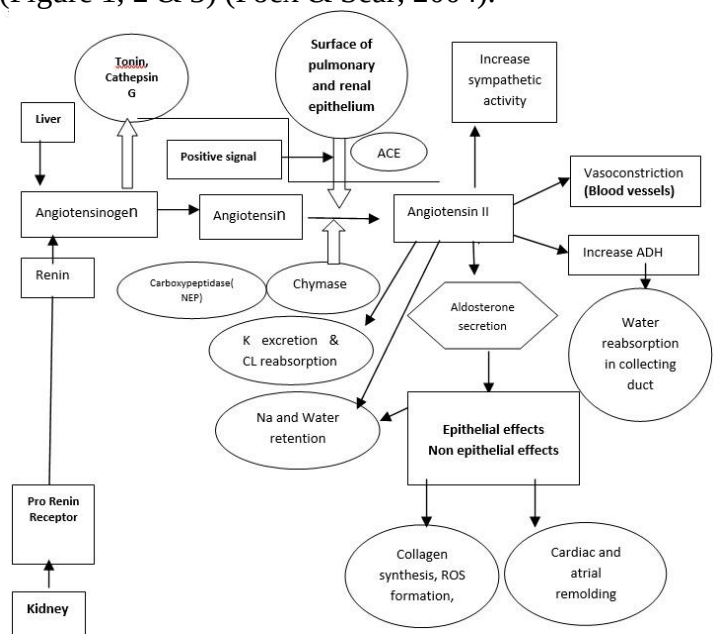

Figure 1: Interplay showing renin angiotensin system mechanism, therapeutic targets and role in hypertension (Foëx & Sear, 2004).

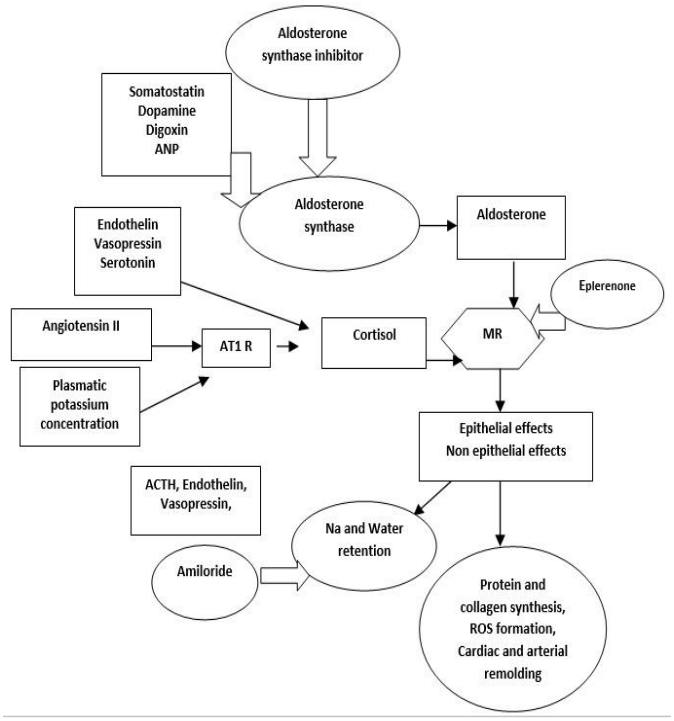

Figure 2: Possible therapeutic options in aldosterone mechanism in the control of hypertension

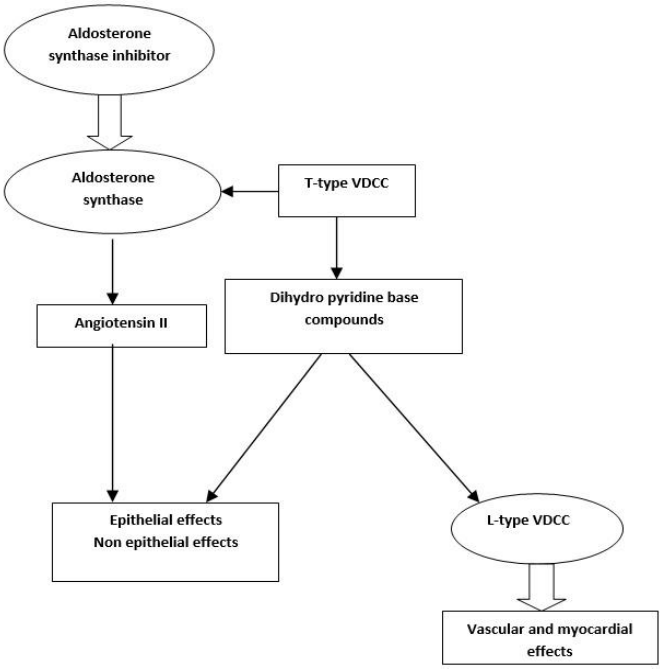

Figure 3: Promising therapeutic targets in aldosterone pathway for hypertension management

Renin which is the initiator of cascade, released from kidney cleaves the liver-produced angiotensinogen to angiotensin I (Ang I). Renin become attached to its (pro) renin receptor (P)RR that enhances its cleavage activity and activates itsinactive precursor, prorenin. Angiotensin I, the product of renin activity, is hydrolyzed by angiotensin converting enzyme (ACE) to the active angiotensin II (Paulis & Unger, 2010). ACE is the circulating and locally expressed enzyme which is fundamental for this cleavage. Angiotensin-converting enzyme also inhibits vasodilating and stimulating activity of nitric oxide (NO) and prostacyclin (PGI2) by inactivating bradykinin. Alternatively, angiotensin-I is cleaved by enzyme chymase. Moreover, another pathway of direct cleavage of angiotensinogen to angiotensin II is tonin and cathepsin G enzymes and carboxypeptidases (NEP), important markers of future target as well (Fyhrquist & Saijonmaa, 2008).

Physiology of sympathetic nervous system in hypertension

Amplified sympathetic nervous system activity increases blood pressure (Oparil *et al*., 2003).It is the key determinant of blood pressure variableness (Mancia & Grassi, 2014). Through the stimulation of the heart, peripheral vasculature and kidneys it contributes to the progress and maintenance of hypertension causing increased cardiac output, increased vascular resistance and fluid retention (Oparil *et al*., 2003). Several ways are thought the cause of SNS overactivity. One of them is that activation of the SNS depends on the circulating angiotensin II concentrations, predictable to exert excitatory effects on sympathetic steady flow and augment adrenergic receptor receptiveness to stimuli by ease of NE (norepinephrine) release from adrenergic nerve endings (Mancia *et al*., 1999). Another cause is insulin resistance which results in

hyperinsulinemia known to either increase sympathetic nerve transaction or to stimulate NE oozing from the sympathetic nerve endins that simultaneously augument BP. However, it should be emphasized that sympathetic activation has in turn been revealed to cause insulin resistance or vice versa so that it is still tentative which of these two alterations precedes and determines the other. Activation of the SNS has a central nature as it depends on an excessive hypothalamic drive due to excessive environmental stimuli and/or an inherent subcortical hyper-responsiveness to an otherwise "normal" environment. The activation of the SNS accompanying hypertension is due to impairment of a reflex that restrains sympathetic tone to an important degree, i.e., the arterial baroreflex. The baroreceptor ability to modulate vagal tone undergoes early impairment, which becomes progressively more evident as HTN becomes more severe (Mancia & Grassi, 2014). Role of sympathetic nervous system on HTN is summarized in (Figure 4).

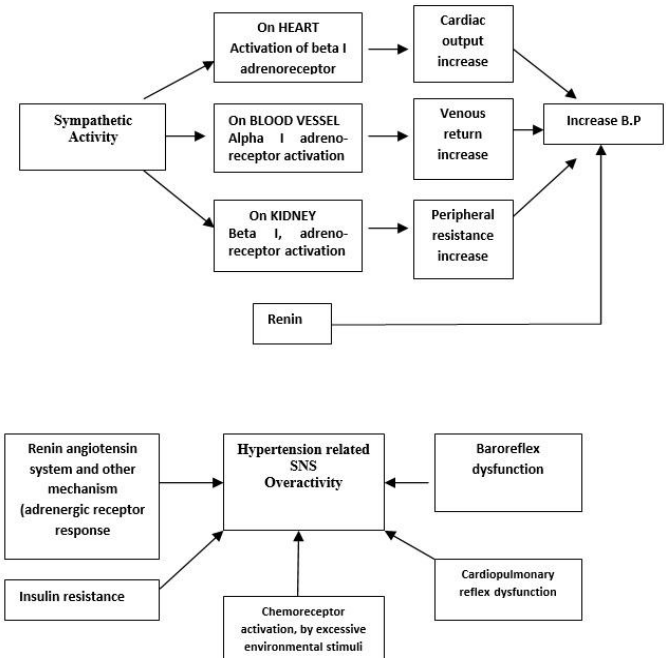

Figure 4: Schematic representation of mechanisms responsible for sympathetic activation in HTN

Current and Novel therapeutic targets:

Renin as a target

Aspartic protease renin (Danser & Deinum, 2005) in the RAAS cascade, catalyzes the rate limiting step, represents a very striking therapeutic target that was lately oppressed by the preface of the first-in-class discriminating renin inhibitor, aliskiren. The lessening of Ang I and Ang II levels with resultant BP reduction is definitely allied with renin inhibition (Nguyen & Muller, 2010). Aliskiren reduce BP comparably to diuretics, ACE–Inhibitors, b-blockers and AT1R blockers. Aliskiren proffer a novel therapeutic target in these pipelines.

Prorenin receptor (P)RR as a drug target

Proteolytic or nonproteolytic activities are involved in activation of prorenin by (endogenous) kallikrein or (exogenous) trypsin or plasmin (Danser & Deinum, 2005). Prorenin activation is concerned with binding to (P) RR. Aliskiren has no impact on inhibition of activation of the (P) RR by (pro)rennin. The specificity for the blockade of (P) RR is a valuable therapeutic option for HTN (Nguyen & Muller, 2010) as this could not only reduce the enzymatic activity but also avoid some Ang-independent effects of renin (Danser & Deinum, 2005). Recently, it has been suggested that handling region peptide (HRP) could be a partial agonist at (P) RR which may have ability to inhibit activation of prorenin. Nonetheless, some authors have recommended that HRP might affects (P)RR whereas another group of investigators have reported that the HRP might have (P)RR-independent effects. So, a unique therapeutic option still exist for development of full agonist at (P) RR (Nguyen & Muller, 2010).

Therapeutic targets in aldosterone antagonism:

Aldosterne synthase inhibitor

Several factors activate aldosterone synthase, angiotensin type 1 receptor as stimulated by angiotensin II, adrenocorticotropin release, endothelin and high plasmatic K^+concentrations (Hargovan & Ferro 2014). Therefore, a best loom to decrease aldosterone level, inhibit aldosterone synthase to avert MR (mineralocorticoid) dependent and MR-independent effects (Fiebeler *et al*., 2005). Numerous aldosterone synthase inhibitors (CYP11B2), Fadrozole, an aromatase inhibitor, its dextroenantiomer (FAD286) has been developed and revealed to inhibit aldosterone synthase and several dihydropyridine Ca^{2+} channel blockers block T-type calcium channels as well as inhibit aldosterone synthesis in vitro (Unger *et al*., 2011)**.** Moreover, it has been reported that to antagonize the MR, Ca^{2+} conversely, have the specificity and potency for aldosterone synthase blockade. But in *in-vivo* studies its effects have not been established clearly. Nevertheless, dihydropyridine structure might be the foundation for the advancement of narrative molecules that have dual effects of blocking aldosterone synthase as well as MR for aldosterone antagonism in company with inhibition of the L-type Ca^{2+} channel for more effectual antihypertensive effects (Unger *et al*., 2011).

Aldosterone receptor antagonist

Aldosterone has established epithelial and non-epithelial actions achieved by its effect on mineralocorticoid receptors important in blood pressure and many other associated activities (White *et al*., 2010). One well-known mineralocorticoid-receptor blocking agents (MRAs) are Eplerenone. Thus, MRAs have become useful in the treatment of hypertension and have provided a new therapeutic option in the past decade and stepped up over the mounting appraisal for the function of aldosteronism in this disease circumstances. Spironolactone, previously used for this purpose has several side effects as compared to eplerenone (Unger *et al*., 2011). Therefore, development of newer chemical entities that target should be appreciated in future. Recently some Ca^{2+}channel blockers have been reported to antagonize the MR as well. This action specific to dihydropyridine derivatives (e.g. nimodipine) might explain their beneficial effect in hypertension and other related disease states as ischemia. Hence, molecules with dual action on MR and Ca^{2+}channels might represent a novel and appealing prospect in antihypertensive therapy and end-organ damage (Dietz *et al*., 2008).

More therapeutic innervations in aldosterone antagonisms:

In low aldosteronism it might be activated by cortisol, so inhibition of cortisol formation provides a narrative approach for therapy. Furthermore, inhibition of epithelial Na ion channel is necessary for controlling B.P as Naretention increases B.P. Recently, amiloride is used for this purpose having fewer side effects.

Vasopeptidase Inhibitors

As Antihypertensive agents, vasopeptidase inhibitors are valuable because they inhibit both ACE and NEP (Divya *et al*., 2011). Beside ACE, NEP and endothelin-converting enzyme (ECE-1) are other metallopeptidases that produce vasoactive substances (Divya *et al*., 2011). NEP is the chief enzymatic trail for deprivation of natriuretic peptides, a secondary enzymatic pathway for degradation of kinins and adrenomedullin. The natriuretic peptides can be thought as endogenous inhibitors of the renin angiotensin system (Corti *et al*., 2001).

Current findings point towards the great impact on combined ACE/ECE inhibitors, however most research has acknowledged the role of NEP and the therapeutic prospective of its inhibition (Unger *et al*., 2011). Synergistic effects including blockade of angiotensin (AT) synthesis, natriuretic peptides along with bradykinin as a result of combined ACE and NEP inhibition leading to vasodilatation, natriuresis and thus improvement in B.P. Omapatrilat has recently been discovered ACE/NEP inhibitor as supported by various animal studies (Corti *et al*., 2001). Effect neutral endopeptidase in B.P control is very modest and variable because of its both vasodilator as well as vasoconstrictor nature (Weber, 2001). However, this dual inhibition may produce side effects as angioedema so in this case a combination of AT1 blocker and NEP give better tolerance profile with no risk of angioedema. So, angiotensin receptor blocker and neprilysin inhibitors, ARNI, LCZ696, a first-in-class ARNI reduce BP and confer atypical target in antihypertensive therapy (Unger *et al*., 2011).

Endothelin system: endothelins and endothelin receptor antagonist

Endothelins, are peptides that constrict blood vessels thus raising the blood pressure normally they are reserved in balance by various mechanisms but when they are over-expressed then they increase blood pressure and cause cardiovascular events. Therefore, endothelin might be a well therapeutic target (Weber *et al*., 2009). However, toxic profile of endothelin antagonisim not gains as such importance, but their role in pulmonary hypertension subsist (Sica, 2008). Three different types of endothelin exist, but role of ET1 has been recognized and its receptor antagonist has most extensively been evaluated (Feldstein & Romero, 2007). Additionally, in different trials, darusentan (ETA/ETB antagonist) has achieved the end-points for systolic and diastolic BP in patients with resistant hypertension. Recently, in various trials selective ETA antagonists or dual AT1R/ETA antagonist [e.g. PS43354} has produced significant reduction in B.P and greater tolerance (Weber *et al*., 2009).

Endothelium derived vasoactive factors as a treatment target in hypertension

Various vasoactive factors, nitric oxide (NO), arachidonic acid metabolites, reactive oxygen species and vasoactive peptides derived from endothelium regulate vascular tone (Förstermann & Münzel, 2006). Furthermore, endothelial dysfunction is a complex disorder, which has been associated with hypertension of assorted etiologies with different pathways and as prospective drug targets for novel treatments in hypertension and end-organ damage (Vanhoutte & Tang, 2008). Importantly, alterations of the L-arginine NO-synthase–soluble guanylyl cyclase pathway have provided various therapeutic targets from the very beginning (Förstermann & Münzel, 2006). Others, EDHF-mediated responses can give a vasodilator store in hypertension and can reimburse, at least momentarily, for endothelial dysfunction due to compromised synthesis or availability of NO. Still another, EDCFs (endothelial derived contracting factors) contribute to endothelial dysfunction related to hypertension by counteracting the effect of endothelial vasodilators and provide important narrative targets for antihypertensive therapy in metabolism of arachidonic acid pathway (Feletou *et al*., 2010). All current and novel therapeutic targets are given in (Figure 5).

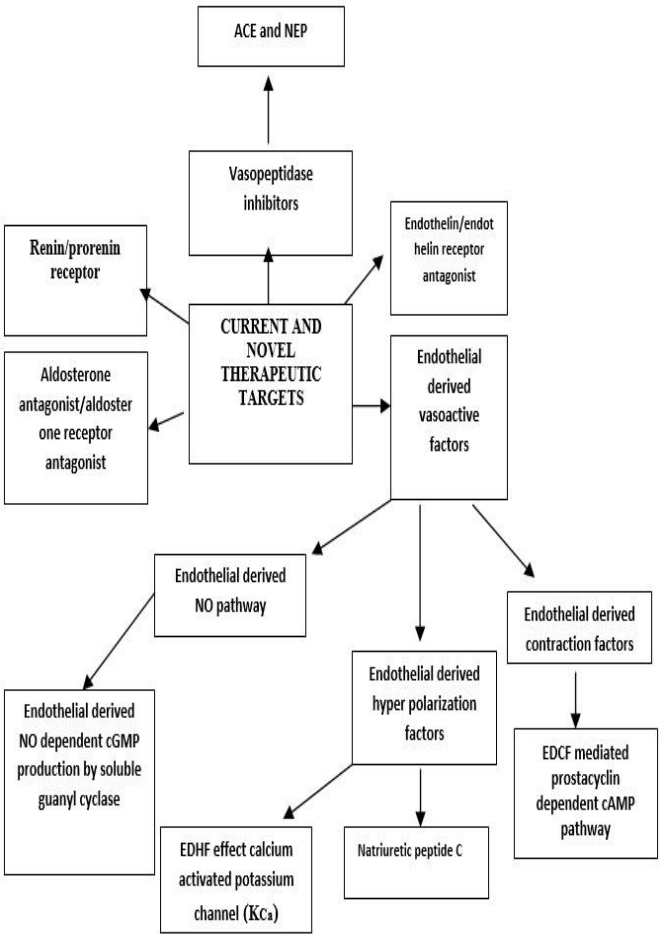

Figure 5: Interplay of current and novel factors in hypertension, endothelial derived vasoactive substances their pathways and targets

Gene based therapeutics:

In the treatment of hypertension, a phase will come where more focus must be sited on other peculiar treatment paradigms rather than advance development of conventional and therapeutic drugs. Unremitting advances in gene delivery systems has come to an end with the Human Genome Project making it attainable to investigate genetic resources for the treatment and possible cure for hypertension (Katovich *et al*., 2005). Gene therapy minimizes side effects and provides the opportunity of producing long-term special therapeutic effects with specificity based on the scrupulous genetic target. In the exposition of the cellular and physiological mechanisms of hypertension two modules of genes have fascinated attention in the development of long-established pharmacological therapies for the disease. They include vasodilatory genes and vasoconstrictor gene as enlisted in (table 3). In actual fact, these genes have major strides in the development of targeted and novel drug, the result of which is effective control of B.P with high and better tolerance profile (Pachori *et al*., 2001).

Table 3: Gene based therapeutics

Vasodilatory genes	Vasoconstrictor genes
Bradykinin	RAS components
Nitric oxide synthase	Adrenergic receptors
Atrial natriuretic peptide(ANP)	Endothelin
	K^{1+}& Ca^{2+} channel

For hypertension, there are two comprehensive gene transfer approaches that have been used effectively. One is an induction or over-expression of genes that lower blood pressure and second is reduction or decreasing the gene products that are known to increase blood pressure. Therefore, to achieve that, sense and antisense gene therapy techniques are used (Katovich *et al*., 2005). Antisense basically used for vasoconstrictor pathways. Among these, RAAS components in regulating B.P are imperative and important for lifelong prevention of hypertension (Katovich *et al*., 2005). RAS as a target of antisense approach give conceptual support for its usefulness in hypertension as its role is well established and well documented for pharmacological agents, gene therapy and can be compared by different protocols (Pachori *et al*., 2001). The antisense targeting of the RAS component (angiotensinogen or the angiotensin [Ang] II type I receptor) would attenuate BP. One such promising result obtained by use of antisense oligonucleotides has resulted in significant

lowering of BP in SHR. Even though, sustained effect was attained by using viral based transfer of gene for lifelong prevention of HTN (Katovich *et al.*, 2005).

The sense approach affects the vasodilatory pathway by over-expressing the vasodilatory genes. The important one is endothelial NO synthase viral gene transfer and over-expression. Others include *ANP*, kallikrein, adrenomedulin genes and in this regard transfer of gene via naked DNA or virus is most effective in different models of animals. The reduction of BP after gene transfer is also accompanied by pathophysiologic changes in major organs. For example, human endothelial nitric oxide synthase plasmid DNA delivery to the SHR induced endothelial mediated responses along with significant increases in urinary and aortic cGMP. On the other hand adenovirus-mediated kallikrein gene delivery to SHR causes decrease of BP in 3 to 5 days as well as significant reduction in urinary protein excretion. These innovative studies have provided a support for the value of the "sense" and "antisense" approach for the control of hypertension. In addition to the above mentioned RAS components, the cloning of renin gene has provide remarkable advances in controlling BP as well as in the study of renin in molecular terminologies and its reaction with angiotensinogen. Likewise, studies of gene-regulatory factors may be future targets for blockade of the renin system in antihypertensive therapy (Morris, 1989).

Device based antihypertensive therapy:

Neurogenic components have central role in various forms of hypertension and sympathetic over-activity. Various mechanisms implicated in the regulation of the sympathetic nervous system is presently leading to novel device based approaches in hypertension treatment which mostly target either a reduction of central sympathetic drive from peripheral chemoreceptor/mechanoreceptor (afferent) or a diminution of renal sympathetic efferent signaling (or both) (Potthoff *et al*., 2011). Therefore, central sympathetic derive can be ablated by barorecept or stimulation and therapeutic renal sympathetic nerve denervation (Krum *et al*., 2011).

Renal sympathetic denervation therapy:

Surgical renal denervation has been shown to be a successful approach of reducing sympathetic outflow to the kidneys by inhibiting renin release, natriuresis, diuresis and abridging afferent, efferent nerves can also decrease sympathetic drive (Dibona, 2003). However, these procedure bare side effects so, catheter based approach has recently been adopted that involve femoral artery catheterization with radiofrequency energy. For this purpose, an initial cohort study has been designed and reduction in office blood pressure was measured as compare to baseline systolic blood pressure of 160mmHg. The reduction of blood pressure is comparable by reduction in sympathetic activity with norepinephrine. Moreover, muscle sympathetic nerve activity (MSNA) has recommended a reduction in afferent sympathetic activity as reflected by reduced central sympathetic drive (Sievert, 2010).

Baroreflex sensitization therapy:

As stated earlier, baroreceptor reflex dysfunction is imperative in many hypertensive diseases as caused by sympathetic over-activity; therefore sensitization of baroreflex is adopted that reduces blood pressure in various animal models. Baroreflex at carotid artery by implanting pacemaker is successful in canion animal model (Potthoff *et al.,* 2011). Moreover, in the Rheos Pivotal Trial, preliminary results have also

confirmed the comparable results in blood pressure control .In both trials animal model have showed a reduction in systolic and mean blood pressure after baroreflex sensitization (Sica *et al*., 2010). In addition to the mentioned above strategies, more advances are still required for effectively targeting the blood pressure.

Vaccine based therapeutics:

Gene based therapies provide a better approach and same results are expected from vaccine based therapy. Recently, identification of two vaccines against angiotensin receptor (PMD3117, Cyt006) has opened a new horizon of investigation and treatment of hypertension (Ambühl *et al*., 2007). An immunological approach might offer alike advantages, even though some disappointments have revealed in various trials. In one trial Cyt006 against Ang II in SHR reduce BP but in some others it not reduced in comparison with existing antihypertensive therapy. PMD3117 did not decrease BP, despite of some extent of RAAS blockade in animal trials. Vaccination or pre-vaccination against renin in some trials is valuable but produce kidney problems. Overall, vaccine based approach in antihypertensive therapy is feasible and effective (Michel *et al*., 1999).

Conclusion:

Hypertension is a highly prevalent health problem all over the world and has become a leading cause of morbidity and mortality in developing countries. Hypertension entails complex pathophysiologic mechanisms making it difficult to initiate selective antihypertensive therapy in any hypertensive patient. Recent treatment guidelines suggest generic approach in the management of HTN with slight emphasis on selective and individualized therapy based on underlying pathophysiology of HTN. Hence, there is a pressing need to develop innovative therapies devoid of shortcomings as associated with conventional treatment. Innovative therapies are directed against specific targets in several pathophysiologic pathways involved in elevation of blood pressure that have not been established therapeutically so far. In this review, an attempt has been made to elucidate numerous novel therapeutic approaches including development of drugs against various enzymes implicated in blood pressure elevation, gene based therapeutics , baroreflex sensitization therapy, Device based antihypertensive therapy, Renal sympathetic denervation therapy and vaccine based therapy. Hence, it is worthwhile to say that development of these narrative therapies might be highly useful for effective and selective control of hypertension thus improving the quality of life in hypertensive patients.

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