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World Journal of Hypertension (*World J Hypertens*, *WJH*, online ISSN 2220-3168, DOI: 10.5494) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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MINIREVIEWS

Roles of catecholamine related polymorphisms in hypertension

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Abstract

The objective of this review is to summarize current data obtained so far in catecholamine-essential hypertension (EH) relationships on a genetic basis. As the major elements driving the sympathetic system's actions, catecholamines modulate a variety of physiological processes and mutations related to the system. This could generate serious disorders, such as severe mental illnesses, stress-induced disorders, or impaired control of blood pressure or motor pathways. EH is idiopathic, and the genetic basis of its causes and substantial interindividual discrepancies in response to different types of treatments are the focus of interest. Susceptibility to disease or efficacy of treatments are thought to reflect genomic variabilities among individuals. Therefore, outlining the available knowledge in functional genetic polymorphisms linked to EH will make the picture clearer and will help to establish future prospects in the field.

Key words: Single nucleotide polymorphism; Catecholamine; Adrenergic receptor; Dopamine receptor; Hypertension; Epinephrine; Norepinephrine

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Core tip: Catecholamines are the major elements of sympathetic system's actions, therefore they also act as important regulators of blood pressure. Polymorphism studies require a tedious approach since there are inconsistencies among the studies due to different ethnical origins, subject size and self discrepancies among individuals. Nevertheless, there are many promising findings and still more fields to investigate. Especially role of genes involved in the biosynthesis and metabolism of catecholamines were relatively missing. This review summarizes the current knowledge about catecholamine-related polymorphisms on the basis of development, prognosis and drug response of essential hypertension and aims to improve better assessment of the disease.

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INTRODUCTION

Catecholamines are the class of molecules containing a catechol ring, which consists of a 2-hydroxyl-attached benzene ring, together with an amine chain. Involving epinephrine (or adrenaline), norepinephrine (or noradrenaline), and dopamine, this class of molecules serves to regulate both metabolic and neural mechanisms in the body and act as important targets for a large group of pharmacological agents.

Adrenaline is a hormone synthesized and released by the adrenal medulla into the bloodstream. Its concentration in plasma can rapidly rise up several-fold under a physical or mental tension, and when a sufficiently high concentration is achieved, it can trigger noradrenaline release from adrenergic terminals, an action indirectly affecting neuronal transmission. Noradrenaline, on the other hand, acts as a neurotransmitter rather than a hormone, though it shares very similar chemical structure with adrenaline, except a methyl group. It is released by neurons in the brain and, similar to adrenaline, it acts through alpha or beta adrenergic receptors. Dopamine is the metabolic precursor of noradrenaline and adrenaline, and it also acts as a transmitter/neuromodulator in the central nervous system through dopaminergic receptors.

As a crucial element of drug actions, catecholamine polymorphisms became a focus of interest in various disorders. Hypertension, one of the most common disease worldwide especially among elderly people, is characterized by high blood pressure (BP) and heart rate, two parameters effectively connected to sympathetic denervation. It is a complex disorder with polygenic and environmental determinants. In the majority of cases, it is idiopathic and there is no clear indication of the source. Therefore, searches for hypertension-related genes, mutations, and polymorphisms will assist in the gene-therapeutic approaches and design of target-based therapies. There are more than 50 genes identified so far through association studies, with the reservation of publication bias from selectivity of positive results and limited genotype-phenotype relation analysis[1].

Since the sympathetic nervous system (SNS) is one of the major mechanisms in the rapid regulation and maintenance of BP, it has been hypothesized that the SNS could have a substantial role in the development of essential hypertension (EH). Catecholamines are the mediators of SNS response, and their release from chromaffin cells or ganglionic neuronal ends would affect myocardiocytes; vascular smooth muscle contraction; blood flow through renal, coronary, and cerebral systems; systolic and diastolic BP, *etc*.

This review will briefly discuss the contribution of genetic polymorphisms in EH by combining known catecholamine-related polymorphisms with the anticipated metabolic and neurologic targets in the regulation of hypertension and will try to accomplish its significance in applications using a combinatorial approach with the available clinical data on that issue. The elements of the SNS, parasympathetic nervous system, and other BP regulators directly or indirectly correlated with catecholamine action and hormonal regulation of BP and heart rate will be overviewed in this perspective based on the current knowledge of the polymorphisms of the relevant elements. It is believed that this compilation will help to integrate current accumulated knowledge on the field, provide a preliminary perspective for the design of future studies, and increase our understanding of the genetic basis of catecholaminergic system components in this one of the most prevalent and complexly structured disorder.

RECEPTOR POLYMORPHISMS

One study has indicated that the long arm of human chromosome 5 contains a cluster of genes presumably involved in BP regulation[2]. This region contains genes encoding the alpha1B (α1B) and beta2-adrenergic (β2) receptors and dopamine receptor type 1A (D1A). The study was conducted with young Caucasians, and showed that this genome region has a significant association with systolic BP. Further studies involved other receptor types as well, with a prominence in β2-adrenoceptors, which will be discussed in detail later.

ALPHA-ADRENERGIC RECEPTORS

The a-adrenergic receptors (α-AR) are classified into two-subtypes: α1 and α2. They are G-protein-coupled receptors, and they activate second messenger systems through the activation of G-proteins (G_q or $G_{i/o}$). α1 mediates vasoconstriction and plays an important role in the regulation of vascular tone, while α2 serves to regulate noradrenaline release from presynaptic terminals.

ADRA1

The human α1A-AR is the predominant α1-AR subtype in vascular smooth muscle, the heart, and the liver. Considering its role in smooth muscle contraction, an early study has investigated the role of a previously determined polymorphism in α1A-AR, Arg492Cys, in normotensive and hypertensive black and white American individuals and determined the allele frequency distribution. Arg492 was found to be significantly higher in African-Americans with respect to Caucasians, but the frequency of the variant Cys492 was similar in normotensive and hypertensive individuals[3].

Another α1A-AR polymorphism, Arg347Cys, was examined in a large sample of the Brazilian population (a total of 1568 individuals were involved in the study)[4]. In this study, the Cys/Cys genotype was found to be significantly associated with hypertension (P = 0.06). Moreover, the response to daily treatment with nifedipine, an anti-hypertensive agent, was found

to be related to the same polymorphism in a Chinese population[5]. The later study noted that patients carrying the Cys347 allele of the α1A-adrenoceptor gene (ADRA1A) had a greater systolic BP reduction than did those carrying two Arg347 alleles of the α1A-adrenoceptor gene (32.5 ± 14.0 mmHg *vs* 27.3 ± 15.5 mmHg, respectively, $P = 0.006$) after daily treatment with an oral dose of 30 mg nifedipine gastrointestinal therapeutic system for 16 d, however, diastolic BP reduction was not associated with the Arg347Cys polymorphism. In addition, no significant associations were observed between BP reduction and two other polymorphisms (Arg16Gly and Gln27Glu) of the beta2-adrenoceptor (*β2-AR*) gene.

When the α1B-adrenoceptor gene (*ADRA1B*) was examined for possible polymorphisms, it was found that polymorphisms of this gene are much rare than expected considering its close location to the genes of β2-AR and dopamine receptors (DR)[2,6]. An amino acid addition at position 368 (368Arg) and a substitution (Arg371Gly) were investigated in a small population of 24 male patients with uncomplicated EH (12 Caucasians, 12 African-Americans) and 21 male normotensive (NT), first-degree relatives of the study group (12 Caucasians, 9 African-Americans)[6]. The study was unable to detect a relationship between these polymorphisms and BP levels or response to phenylephrine, an alpha-agonist used as a decongestant.

The role of the α1D-AR subtype in hypertension development was investigated in mice through a salt-induced hypertension model. The study suggested that α1D-AR plays an important role in developing a high BP in response to dietary salt-loading, and that agents having selective α1D-AR antagonism could have significant therapeutic potential in the treatment of hypertension[7]. To our knowledge, there are no studies reporting an association between ADRA1B or ADRA1D gene variants and hypertension.

A recent genome-wide study has strengthened the role of the adrenergic alpha1 receptor (ADRA1) pathway in hypertension and BP regulation. The ADRA1 pathway showed a strong association with diastolic BP ($P_{path} < 0.0007$) and hypertension ($P_{path} < 0.0009$) than systolic BP ($P_{path} < 0.06$). This pathway consisted of genes involved in adrenaline and noradrenaline synthesis, in vascular smooth muscle cell signal transduction leading to intracellular calcium release, and in major regulatory proteins. The study especially stratified the association of α1B-AR (ADRA1B) and the phenylethanolamine N-methyl transferase (*PNMT*) gene, the enzyme that catalyzes conversion of norepinephrine to epinephrine by the transfer of a methyl group[8]. The paper, however, emphasized the fact that neither of the remaining pathways utilizing the PNMT reached pathway significance, nor did the removal of ADRA1 receptor genes affect observed ADRA1 pathway significance, suggesting that none of the elements could be self-sufficient mediators for the observed associations.

ADRA2

The α2A-ARs are mainly involved in neurotransmitter release from sympathetic nerves. They are found on pre- and post-synaptic neurons of the central and peripheral nervous systems and blood vessels, and their involvement in BP regulation has been reported by various studies[9-11]. Yet, studies investigating the relationship between hypertensivity and different polymorphic sites mostly indicate a lack of association in various ethnic populations.

The α2A-ARs act through the G_i/G_o family of G-proteins, and they help to regulate a wide range of physiologic functions, including vascular, cardiac, and metabolic systems, as well as the central and peripheral nervous systems. Agonist binding to receptors causes the receptor to couple with related G-proteins, which in turn initiates effector responses like the inhibition of adenylyl cyclase or the activation of phospholipase C. Pre-synaptic activation of α2-adrenoceptors in sympathetic nerve endings and noradrenergic neurons leads to inhibition of norepinephrine release. Central nervous system activation of post-synaptic α2-adrenoceptors inhibits sympathetic activity, which results in hypotension and bradycardia, as well as sedation. Therefore, α2 agonists could be potent antihypertensive agents. Higher doses of α2-AR agonists, on the other hand, activate smooth muscle receptors in the arterial resistance vessels and could produce hypertension[12].

The BP and other responses to α2-AR agonists and antagonists can show high variability among individuals depending on the population pool. Like other signaling systems, variations can involve different elements through the signaling pathway, like G-proteins or effector enzymes, which will be discussed later. On the receptor side, a single nucleotide polymorphism (SNP) of α2-AR, which results in Asn-to-Lys substitution at amino acid 251 of the third intracellular loop (position 753), was identified in a study conducted by Small *et al*[13]. Subsequently, a total of 376 individuals (125 + 99 NT, 75 + 77 HT for Caucasians and African-Americans, respectively) were genotyped for this locus. The frequency of Lys-251 was 10-fold greater in African-Americans than in Caucasians, but was not associated with EH. Since the third intracellular loop forms the main site of G-protein interaction, the functional role of this substitution was also examined in a cell expression system. There were no detectable changes in ligand binding and basal function, but [^{35}S] GTPgammaS binding was 40% greater in Lys251 form. The findings implicated that this small replacement represented a gain of agonist-promoted function with enhanced inhibition of adenylyl cyclase, activation of MAP kinase signaling, or stimulation of phospholipase C/inositol phosphate pathways.

Based on these observations, it can be said that α1A-AR polymorphisms R347C and R492C significantly contributed to BP regulation. There is an ongoing research related to the other SNPs in α1A as well as

α1B and α1D subtypes and further investigations are needed to accurately assess their roles in hypertension.

β-ADRENERGIC RECEPTORS

The b-adrenergic receptors couple to either G_s or G_i (heterotrimeric stimulatory and inhibitory G-proteins) proteins. β1-ARs are the predominant type in the sympathetic control of heart rate and myocardial contraction. Protein kinase A, activated through the β1-AR → Gs → adenylate cyclase (AC) → cyclic adenosine monophosphate (cAMP) pathway, phosphorylates a set of regulatory proteins in cardiac excitation-contraction coupling, such as L-type Ca^{2+} channels or SERCA proteins. β2-ARs cause smooth muscle relaxation and bronchodilation. Defective β2-mediated vasodilation could result in both increased arterial resistance and reduced venous compliance. β-ARs are effectively used as targets to exogenously administered inhibitory agents, known as β-blockers. The β3 receptor, a relatively novel subtype, is mostly found in brown adipose tissue and plays role in the enhancement of lipolysis in this tissue, and is also responsible for thermogenesis in skeletal muscles.

ADRB1

There are many SNPs identified in the gene of β-ARs corresponding to different parts in structure[14]. Functional SNPs related to BP regulation were Ser49Gly at the N-terminus and Arg389Gly at the C-terminus of β1-AR. Three genetic polymorphisms, one of which belongs to the β1-AR, were investigated in Japanese hypertensive subjects by Shioji *et al*[15]. The polymorphisms alpha-adducin (ADD1/Gly460Trp), β1-adrenoreceptor (ADRB1/Arg389Gly), and G-protein β3 subunit (GNB3/C825T) were screened in 867 males and 1013 females. The ADRB1/R389G polymorphism and hypertensive status in male subjects were close to the significance (P = 0.0702). ADD1/G460W polymorphism was associated with hypertension in female subjects, and the GNB3/C825T polymorphism was not associated with hypertensive status in either male or female subjects. None of the polymorphisms was significantly effective on the disease. The relationship between the two polymorphisms (Ser49Gly and Arg389Gly) and BP or heart rate was also tested in a small group of patients (101 subjects) with EH and left ventricular hypertrophy treated with β1-AR blocker atenolol for 12 wk. Though reduction in heart rate was greater in Gly49 patients compared to the Ser/Ser genotype, there was no significant effect detected on heart rate and BP[16].

ADRB2

At 1998, Timmermann *et al*[17] reported four intragenic variants at the promoter region and N-terminus of the β2-AR in a study involving the offspring of 23 hypertensive and 22 normotensive European families. These mutations were a C→T substitution at -47 in the 5′ cistron causing Arg→Cys exchange, a T→C substitution at -20, and an A→G substitution at +46, resulting in Arg→Gly exchange of amino acid at 16 and a C→G substitution leading to Gln→Glu exchange at amino acid 27. All variants were found to be in linkage disequilibrium, but in particular the position -47 variant was significantly higher in frequency in the offspring of hypertensive parents, and Arg16Gly at +46 was significantly associated with parental hypertension and higher BP in this sample pool. Later studies further supported this relationship, mostly focused on the Arg16Gly and Gln27Glu substitutions, which introduce a change on the extracellular part of the receptor; however, as the data accumulated from then, so did contradictive findings. In order to compare study outcomes, a summary of cumulative data according to the ethnicity, study size, and allele distributions for β2-AR is introduced in Table 1[18-30].

Studies were also conducted to determine if β2-polymorphisms have an effect on response to antihypertensive reagents. Benazepril is an angiotensin-converting enzyme (ACE) inhibitor used primarily in the treatment of hypertension, congestive heart failure, and heart attacks. A study investigated the role of Arg16Gly polymorphism on systolic and diastolic BP s (SBP and DBP) before and after a 15-d benazepril treatment in a Chinese population that consisted of a total of 931 hypertensive subjects, and showed that ADRB2 R16G polymorphism may play an important role in DBP response to benazepril treatment[31].

ADRB3

The most widely studied β3-AR polymorphism is the missense mutation at position 64, which replaces tryptophane at this position with arginine. This polymorphism was found to be linked with high body mass index and obesity[32-34]. A white population (German) with type 2 diabetes carrying the Arg variant had higher BP and was more hypertensive, though they admitted to intense antihypertensive treatment[35]. Likewise, a similar study conducted in a large unselected Southern Italian population involving 979 patients showed that carriers of the Trp64Arg genotype were more often in the upper one-third of abdominal adiposity and were more hypertensive than the Trp64Trp homozygotes[36].

Several polymorphisms previously reported as risk factors in elevated BP and hypertension-ADRA1B, ADRA2A, ADRB1, and ADRB2-were examined in relation to systolic and diastolic BP s and heart rate, both at rest and in response to stress, by McCaffery *et al*[37]. Subjects (350 normotensive individuals) of European-American origin were analyzed for their BP s and adrenergic receptor variants at seven sites. At position 1165 of the *ADRB1* gene (Gly386Arg), G allele carriers showed higher systolic and diastolic BPs compared to homozygotes for the C allele. In addition, the AA genotype at position 145 of the gene (*Ser49Gly*) was found to be associated with SBP and DBP. At position 46 of the *ADRB2* gene (Arg16Gly), GG homozygotes had

Table 1 List of recent studies on β2-adrenergic receptor polymorphisms, blood pressure and hypertension

SNP	Ref.	Ethnicity	Sample size (HT/NT)	Association/ significance	Parameter
Arg16Gly	Kotanko *et al*[18] 1997	African Caribbeans	136/81	Yes	Hypertension
Arg16Gly	Gratze *et al*[19] 1999	Austrian Caucasians	57 NT	Yes	Blood pressure regulation
Gln27Glu Arg16Gly	Candy *et al*[20] 2000	Black South African	192/123	No	Hypertension, blood pressure Left ventricular mass
Gln27Glu Arg16Gly	Bray *et al*[21] 2000	Non-hispanic whites	589 families (> 2000)	Yes	Hypertension systolic, diastolic and mean arterial pressure
Gln27Glu Arg16Gly	Jia *et al*[22] 2000	Caucasians	298/298	No	Hypertension
Gln27Glu Arg16Gly	Xie *et al*[23] 2000	Black or white Americans	356/307	No	Hypertension
Arg16Gly	Herrmann *et al*[24] 2000	Black or white Americans	243	No	Hypertension
T-47C Gln27Glu Arg16Gly	Kato *et al*[25] 2001	Japanese	842/633	No	Hypertension
T-47C Gln27Glu Arg16Gly	Ranade *et al*[26] 2001	Chinese	> 800/> 800	Yes (only for Arg16Gly)	Hypertension
Gln27Glu Arg16Gly Thr164Ile	Tomaszewski *et al*[27] 2002	European (Polish)	638	No	Hypertension
Gln27Glu Arg16Gly Thr164Ile	Pereira *et al*[28] 2003	Brasilian	1576	Yes	Hypertension, blood pressure
Gln27Glu Arg16Gly	Galletti *et al*[29] 2004	Non-selected group-middle aged men	405 HT 563 overweight	No	Hypertension, overweight
T-47C Gln27Glu Arg16Gly	Ge *et al*[30] 2005	Han Chinese	503/504	Yes	Hypertension

SNP: Single nucleotide polymorphism; HT: Hypertensive ; NT: Normotensive.

higher resting DBP and AG heterozygotes had lower SBP than other genotypes.

Considering the close relationship between obesity and high BP, polymorphisms of β2 and β3 were investigated in a group of Japanese subjects (1121 men), selected as overweight or obese but not having diabetes mellitus or hypertension. The findings of the study demonstrated that the Arg64 allele of β3 and the Gly16 allele of β2 could have an indicatory role to predict weight gain-induced BP elevation in obese subjects[38]. Similarly, a total of 437 Chinese subjects, including 149 obese hypertensive patients and 139 non-obese essential hypertensive patients, were genotyped to investigate the association between Trp64Arg, Arg16Gly, and Gln27Glu polymorphisms and the susceptibility to obesity and hypertension in a Chinese population. The data revealed that the frequencies of β3-AR 64Arg and β2-AR 27Glu were significantly higher in obese hypertensive patients than in the non-obese hypertensive population[39].

The distribution of β-receptor polymorphisms was also determined in hypertension-related complications, such as left ventricular hypertrophy and arterial stiffness. In a group of 300 patients, pulse wave velocity and hyperemia was found to be associated with Ser49Gly of β1-AR, while left ventricular hypertrophy was more related to Glu27Gln β2 polymorphism, suggesting that these two polymorphisms have an effect on the development of arterial stiffness and left ventricular hypertrophy in EH[40].

BP response to the β-blocker atenolol administered 50 mg twice a day was examined in association with hypertension-related and closely linked SNPs of the β1-adrenergic receptor (Ser49Gly and Arg389Gly) and the β2-adrenergic receptor (Cys19Arg, Gly16Arg and Gln27Glu), together with G-protein β3-subunit (A3882C, G5249A and C825T) in EH patients. None of the SNPs were found to be associated with EH, except GNB3 SNPs and BP responses in females[41].

β-AR mutations are preeminent in BP regulation and EH compared to other adrenergic receptor subtypes. β-blockers are the well known medications in cardiovascular disorders. A large family of antagonists, such as oxprenolol or pindolol, are in current use to

block or suppress epinephrine or norepinephrine-mediated actions of the sympathetic system. These lower the heart rate, the force of contraction and reduce the BP. Therefore, it is no surprise that primary antihypertensive effects of adrenergic receptors belong to the β-AR family. Arg16Gly and Gln27Glu are likely to be potential genetic factors to consider and worthy of attention. Positive associations were reported in large scale Chinese cohorts, but studies conducted in other populations are rather inconsistent and should be supported with further analyses.

DOPAMINE RECEPTORS

Dopamine is a neurotransmitter with a variety of roles, majorly in the brain, but also throughout the body. In the brain, it mediates reward-motivated reactions, and helps to produce coordinated motor output, neuro-endocrine regulation, *etc*. Thus, several important diseases, like Parkinson's or schizophrenia, are highly interfered with dopamine activity. Outside the brain, it acts as a vasodilator in blood vessels, and in kidneys it controls renal sodium excretion.

Dopamine receptors are classified into two families: D1-like (includes D1 and D5) and D2-like (includes D2, D3, and D4). Both D1- and D2-like receptors mainly exist in the central nervous system, as well as on the smooth muscle of renal arteries, the juxtaglomerular apparatus, and the tubules of the kidney and cardio-pulmonary system. Like adrenergic receptors, they are G-protein-coupled receptors with seven transmembrane domains. Both members of the D1-family, D1 and D5, could interact with stimulatory G_s, but coupling with other members of G-proteins can be different for each subtype. For example, D1 can also interact with G_o, participating in the regulation of ion channels like Ca^{2+}, K^+, and Na^+, while D5 can couple to G_z members.

The activation of AC through G_s will cause activation of protein kinase A, which in turn will phosphorylate target proteins. In kidney proximal tubules, phosphorylation of two proteins by PKA, the Na^+-H^+ exchanger (NHE), and Na^+-K^+ ATPase (NKA) will inhibit their activation and affect sodium transport across tubules.

The relationship between salt intake and the development of hypertension, together with the renal functions of the dopaminergic system, brought dopaminergic receptor polymorphisms into attention in hypertension research. In 2000, Sato *et al*[42] screened 131 Japanese EH subjects for the A-48G polymorphic site in the DRD1 gene and showed that EH patients carrying the G allele had a higher diastolic BP in general. Later, the allele frequencies of two SNPs, A-48G and G-94A, were determined in a larger cohort, consisting of 493 hypertensive Caucasian subjects. In contrast to the study involving Japanese patients, this study was unable to show any correlation with hypertension in this population, reflecting the role of ethnicity in polymorphism-related secondary effects[43].

When renal clearance of sodium was taken into consideration, the DRD1 polymorphisms A-48G, G-94A, and C-800T were shown to have an effect in the reabsorption of sodium, especially from distal tubules. In a multivariate association analysis, it was shown that DRD1-94GG homozygotes had lower reabsorption rates. The transmission of the DRD1 AGC haplotype was found to be associated with lower systolic and diastolic BP in a family-based analysis[44]. In a small Turkish cohort involving 101 EH patients run by our group, we were not able to obtain such a correlation with the same SNPs (A-48G and G-94A), suggesting that further analysis is required to clear the picture[45].

Dopamine D2 receptors act through G_i proteins, and their inhibitory action on AC reduces the noradrenaline release from sympathetic nerve terminals. Rosmond *et al*[46] examined a common polymorphism in the coding region, an NcoI site in exon 6 (position 1128) in relation to BP and personality disorders. They found that NcoI site polymorphism of DRD2 is associated with BP, and that the TT genotype was significantly more frequent in hypertensive subjects (284 randomly selected 51-year-old Swedish men) compared to controls.

Obviously, one big gap to be filled is the relation of dopaminergic system variants with hypertension. So far, just a few SNPs have been explored and shown to be associated with EH. Effects are mostly through salt transport in the renal tubules and A-48G in DRD1, in particular, have confirmative data. There are not many available data concerning dopaminergic receptor subtype polymorphisms and in view of its role in the SNS, this field should be considered more extensively in future studies.

OTHER FACTORS

As mentioned previously, catecholamines are the major contributors of SNS actions and the cathecholaminergic system is an essential component for the performance of SS activities. There are many enzymes involved in the biosynthesis of catecholamines, which occurs in the chromaffin cells of the adrenal medulla and post-ganglionic fibers of the SNS (Figure 1). The removal of secreted molecules requires mainly actions of two enzymes, monoamine oxidase and catechol-O-methyltransferase (COMT), but also other downstream enzymes, like aldehyde dehydrogenase or aldehyde reductase (Figures 2 and 3). Synthesized catecholamines are stored in vesicles, where stabilization of the vesicle core requires other supportive peptides, like chromaganine[47]. There are also presynaptic transporters that help to remove released molecules from the synaptic cleft back to the presynaptic terminal; these transporters are the targets for drugs of abuse[48]. To our knowledge, there is no report affirming the role of transporter polymorphisms in BP levels or hypertension development, except some preliminary studies suggesting a predisposition[49].

In action, catecholamines act through their receptors and start signal transduction. As mentioned above,

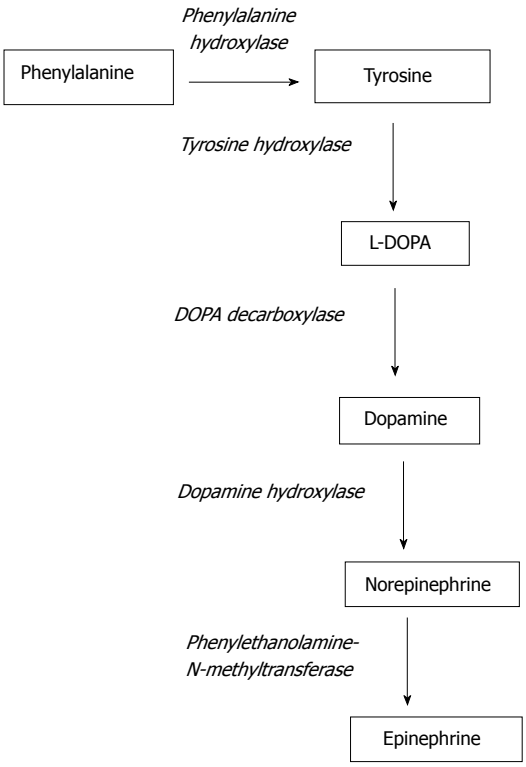


Figure 1 Outline of catecholamine biosynthesis.

catecholamine receptors belong to the GPCR family, and they couple with heterotrimeric G-proteins, finally ending with the activation of protein kinases. There are many proteins taking place on these signal transduction pathways, reflecting the complexity and limited power of association studies. In this large frame of action, the effects of polymorphisms related to the system are too rich to cover in full perspective. In the context of BP and hypertension, however, some important factors are presented by several groups as strong candidates worthy of mention, and will be summarized briefly in the rest of the manuscript.

BIOSYNTHESIS-RELATED FACTORS

The first step in the biosynthesis of dopamine is the formation of L-DOPA, a dopamine precursor, from the amino acid tyrosine by the enzyme tyrosine hydroxylase (TH). TH is the rate-limiting enzyme in catecholamine synthesis. Recent studies have indicated that several polymorphisms of the *TH* gene contribute to BP regulation. Two SNPs at the promoter region of the gene, C-824T and A-581G, were found to be strongly associated with higher BP under stress[50]. In 2010, it was shown that these replacements seriously alter TH promoter activity[51,52]. In accordance with this, Nielsen *et al*[53] reported that the -824T allele increased the relative risk of hypertension by 45%[47]. A study involving 1266 hypertensive subjects searched for the effect of C-824T of TH in hypertension, in addition to the two loci of chromogranin A (CHGA). CHGA is a

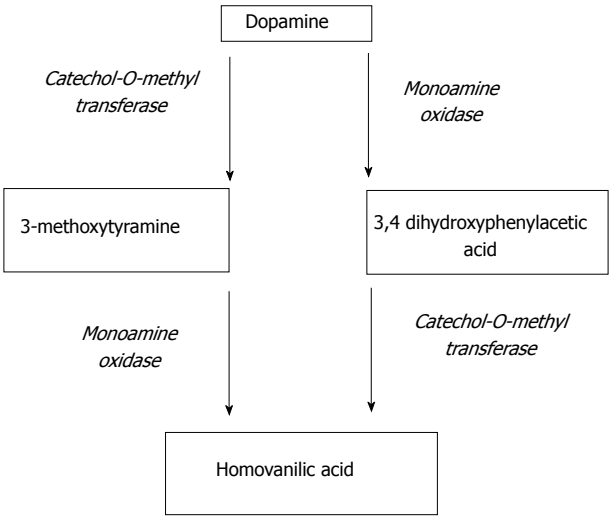


Figure 2 Enzymatic degradation process of dopamine.

peptide located in storage vesicles, and early reports have displayed a strong association between 3'-UTR (C +87T) and EH[54,55]. CHGA polymorphism predicted the risk of developing hypertensive kidney disease in African-Americans. Homozygosity for the minor alleles at T-1014C, T-988G, and G-462A at the promoter region of CGHA exhibited lower stress-induced BP elevations[56].

Another SNP localized to the dopamine hydroxylase promoter, C-970T, was also found to be related with the risk of developing hypertension[57]. More recently, genetic variations of the *PNMT* gene in relation to hypertension were reported in several studies. The distribution of two SNPs, G-367A (rs3764351) and G-161A (rs876493), together with their haplotypes, was screened in 316 pairs of HT and NT patients. Two SNPs' AA haplotypes were found to be less common in hypertensives and therefore suggested to be correlated with the decreased risk of EH in the Han Chinese population[58].

METABOLISM-RELATED FACTORS

The degradation of secreted catecholamines to prevent prolonged stimulation of SNS is very important for the modulation of physiological processes, involving BP and related cardiac functions. Renalase, a novel flavin adenine nucleotide-dependent amine oxidase, is secreted by the kidneys; it helps to reduce the circulating catecholamine concentration. Eight selected SNPs of the renalase gene were genotyped in 503 cases, and three SNPs - rs2576178, rs2296545, and rs2114406 - showed significant associations with EH[59]. The frequency of allele A for rs2576178 in patients with hypertensive and concomitant coronary heart disease was markedly higher. Similarly, the frequency of the C allele of rs2296545 was higher in hypertensives, showing that both genotypes may be contributing to the development of hypertension and chronic heart

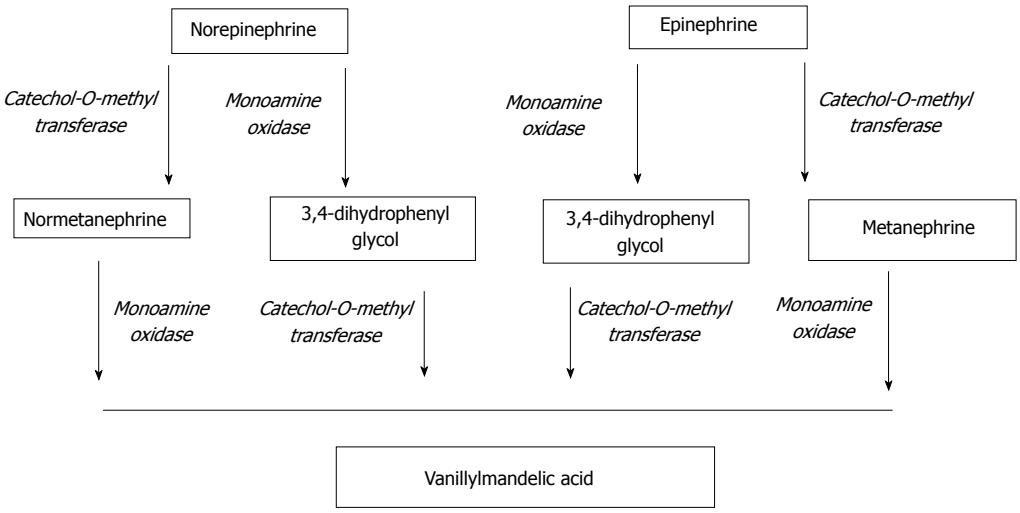


Figure 3 Enzymatic degradation process of epinephrine and norepinephrine.

disease[60].

There were inconsistent results with respect to the *COMT* gene variant *Val158Met* and hypertension. A study on a Japanese population, involving 735 men, showed that the Met allele is associated with higher BP and higher prevalence of hypertension in Japanese men[61]. Another study on a Chinese population, including 215 hypertensive patients, did not detect such a relationship[62]. In the 1995-1997 Word-Trøndelang Health Study (HUNT) group involving 2591 individuals, the Val/Val genotype was found to be more frequent among individuals with hypertension[63].

SIGNAL TRANSDUCTION

A single-base substitution of C825T in exon 10 of the gene encoding the G protein β3 subunit of heterotrimeric Gi proteins (GNB3) was found to be associated with hypertension[64]. This polymorphism leads to alternative splicing of exon 9 and has been associated with enhanced Gi signaling and ion transport[64,65].

Enhanced G-protein-mediated signaling resulting from the truncated C825T form of the G-protein β-subunit may cause high BP as a result of increased NHE activity in tubules, elevated calcium concentration in the cytoplasm, and increased contractility[66].

A large accumulation of studies is present in the literature, strongly supporting the role of C825T in hypertension[64,67-70]. Although the majority of studies has shown an association between the 825T allele and hypertension, there are some contradicting reports, especially in subjects of African and Asian origin, again emphasizing the importance of ethnic origin. Two studies performed by our group also showed that the frequency of the 825T-allele was higher in hypertensive subjects compared to that of controls, and that the difference was statistically significant[71,72].

Recent studies report that the effect of the dopaminergic system in hypertension is mostly due to the impairment of the intrarenal dopaminergic system, and one of the major players is the GRK4, a serine/threonin G-protein receptor kinase, which initiates a desensitization process of the receptor and prevents constitutive activity. Functional polymorphisms of this protein could enhance GRK4 activity, which will reduce dopamine receptor transduction. Increased GRK4 activity also increases angiotensin Ⅱ AT1 receptor activity that is associated with EH[73].

In a small cohort involving 100 EH patients, three gene variants of GRK4 (R65L, A142V, and A486V) were found to be associated with antihypertensive treatment responses[74]. The responses of homozygous double variants of 65L and 142V in particular were much less than the other variants. In another study consisting of 168 Caucasian EH patients, the V allele of the A486V variant was shown to be associated with hypertension and systolic BP[75]. A much larger cohort consisting of 934 whites and African-Americans (44.2%) was also investigated for three proteins of GRK4; it was determined that the 65L allele had a significant effect on systolic BP[76].

Overall, among the synthesis, degredation and signal transduction pathways, there are several replacements possibly involved in the development and progression of hypertension. The most established and well-characterized of these is the C825T mutation in the heterotrimeric G-protein β-subunit. Tyrosine hydroxylase, the primary enzyme for the synthesis of catecholamines, and GRK4, an ezyme with a vital role in salt-transport through regulation of dopamine receptor activity, are conspicuous factors in the assessment of the disease.

CONCLUSION

In the new guidelines released by the European Society of Hypertension (ESH) and the Eurpean Society of Cardiology (ESC), hypertension have been re-

evaluated in the context of its role as a risk factor for cardiovascular diseases[77,78]. Among the previously defined or recently added parameters, individualized therapy approaches are a major concern to estimate overall risk for the patient for the determination and application of the most appropriate treatment and drug regimen[79]. In this perspective, genetic factors need to be well-characterized since they are important contributors of individualized risk assessments.

Regulation of BP coulpatient for the determination could be enhanced and related cardiovascular damage could be reduced if predictors are properly stratified.

As stated above, this review has been restricted to the genetic polymorphisms determined in the catecholamine pathways in relation to BP regulation and hypertension. The selected works contained mostly either positive association studies, unique studies, or a few rare reports in the field of interest. Most of the works in the field are relatively novel, and there is a great number of vacancies to be filled out.

Polymorphism studies always have drawbacks causing them to have inconsistent results, such as ethnicity, sample power, sex, polygenetic factors or linkage effects, and, in the case of drug response studies, periods and consistencies of applied treatments, the reliability of control groups, *etc.* Nevertheless, as will be recognized from the aforementioned reports, the findings are quite remarkable, and a number of studies coincide closely in the outcomes; several variants are highly promising in their potential as predictive markers to estimate the susceptibility of patients to developing hypertension or negative responses to anti-hypertensive drug treatments. As genome-wide association studies are added up, more reliable predictions and their clinical relevance will be achievable, leading the way to more appropriate risk assessments.

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