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Pharmacogenetics: Therapeutic regimen in hypertension

Joshua Ivan Orona Ceron [1], Kevin Salais Diaz [1], Mariela Aketzali Salazar Herrera [1], Dariana Yulian Silva Vargas [1], Lidia Teresa Velázquez Rojas [1] and Brissia Lazalde Medina [2,*]

[1] *Faculty of medicine and nutrition Juárez University of the State of Durango., Durango, Dgo. México.*
[2] *Department of genetics, Juárez University of the State of Durango., Durango, Dgo. México.*

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Abstract

Pharmacogenetics in hypertension is a field of study that aims to understand how interindividual genetic variability can influence the response to medications used to treat high blood pressure, which is a common cardiovascular condition. This approach aims to analyze the pharmacogenetic impact on arterial hypertension.

Currently, a wide range of genetic variants have been identified that can affect an individual's response to antihypertensive medications. For example, some genes can influence how the body metabolizes medications, affecting the dosage needed to achieve adequate blood pressure control. Other genes may be related to susceptibility to adverse side effects.

Pharmacogenetics in hypertension allows doctors to make more informed decisions about which medication to prescribe to a patient based on their genetic profile. This can increase the effectiveness of the treatment and reduce the likelihood of unwanted side effects. Additionally, this approach may be particularly useful in cases of refractory hypertension, where patients do not respond to conventional therapies.

Pharmacogenetics in hypertension is a growing field that seeks to personalize the treatment of this common cardiovascular condition. By understanding how individual genes affect responses to medications, doctors can make treatments more precisely to improve blood pressure control and reduce side effects. However, it is important to note that, although promising, this approach is still in development and is not widely available in clinical practice.

Keywords: Pharmacogenetics; Interindividual variability; Pharmacodynamics; Hypertension

1. Introduction

Blood pressure, commonly known as arterial pressure, is the quantification of the force exerted by the circulating blood in the body against the arterial walls as the heart pumps it. This hemodynamic parameter consists of two phases: a systolic phase corresponding to the contraction of the myocardium, followed by the diastolic phase, which is part of the cardiac relaxation [1]. The regulation of blood pressure (BP) is a complex physiological process involving genetic, epigenetic, and environmental factors.

When there is abnormal blood flow with elevated pressure, it is considered a medical condition that can lead to hypertension, a common medical condition that is characterized for its high morbidity and mortality since it contributes to cardiovascular diseases, heart failure, cerebrovascular diseases, and more [2]. This article focuses on arterial hypertension (AH), defined as the constant elevation of blood pressure [1]. It is a chronic disease with a multifactorial etiology, including genetic factors in the majority of cases (95%) [3]. AH does not usually have a single cause, but is

* Corresponding author: Brissia Lazalde Medina

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polygenic and multifactorial in origin. Only 5% of AH cases are caused by a mutation in a single gene, following a Mendelian inheritance pattern, or environmental factors such as obesity, sedentary lifestyle, tobacco use, diet, etc., can contribute to it, disrupting the delicate balance maintained by various homeostatic factors in blood pressure [3]. (Table 1)

The homeostasis of blood pressure is orchestrated by an intricate regulatory network within the body to safeguard optimal hemodynamic parameters. This regulation is achieved through nervous mechanisms of the autonomic nervous system mediated by baroreceptors stimulation located in major vessels like the carotid sinus and the aortic arch. However, pharmacological intervention is often required to achieve desired therapeutic outcomes in hypertensive patients. (figure 1)

2. Regulation of blood pressure by the renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system consists of a sequence of reactions designed to help regulate blood pressure. When blood pressure decreases (to 100 mm Hg or less for systolic), the kidneys release the enzyme renin into the bloodstream. Renin cleaves angiotensinogen, a large protein circulating in the bloodstream, into two fragments. The first fragment, angiotensin I, which is relatively inactive, is further cleaved into fragments by the angiotensin-converting enzyme (ACE). The second fragment is angiotensin II, a highly active hormone.

Angiotensin II causes constriction of the muscular walls of arterioles, increasing blood pressure. Angiotensin II also triggers the release of the hormone aldosterone by the adrenal glands and vasopressin (an antidiuretic hormone) by the pituitary gland.

Aldosterone and vasopressin (antidiuretic hormones) cause the retention of sodium. Aldosterone also prompts the kidneys to retain potassium. Increased sodium levels lead to water retention, thereby increasing blood volume and blood pressure. (figure 2)

Despite the availability of multiple medications, pharmacogenetic studies, a science used to describe the influence of genes on drug efficacy and side effects, have shown that individual genetic variations influence their response to different medications, in this case, antihypertensive drugs [5]. This results in ineffective treatments and a low rate of blood pressure regulation. Decrypting this link between genetic constitution and pharmacological interaction is imperative to understand interindividual variability and their propensity for drug response. This interaction is broadly regulated by pharmacokinetic mechanisms, which influence drug circulating concentrations and interactions with the target site, including absorption, distribution, metabolism, and excretion processes. Similarly, pharmacodynamic mechanisms dictate the interaction between receptor-drug dynamics and their subsequent outcomes, whether therapeutic or adverse [6,9]. (Table 2)

The goal of pharmacotherapy is to achieve the desired beneficial effect with minimal adverse effects. When selecting a drug for a patient, the clinician's duty is to determine the dose that most closely approximates this goal. A rational approach to achieve this must combine the principles of pharmacokinetics with pharmacodynamics to clarify the dose-effect relationship [6].

Pharmacodynamics regulates the concentration-effect part of the interaction, while pharmacokinetics deals with the dose-concentration part. The pharmacokinetic processes of absorption, distribution, and elimination determine how rapidly and for how long the drug will act in the target organ. The pharmacodynamic concepts of maximal response and sensitivity determine the magnitude of the effect at a particular concentration [6].

Knowing the relationship between dose, drug concentration and effects allows the clinician to take into account the various pathological and physiological characteristics of a particular patient, which make him different from the average individual in response to a drug. The importance of pharmacokinetics and pharmacodynamics in patient care rests on the enhanced therapeutic benefits and reduced toxicity that can be achieved with the application of these principles [6]. (figure 3)

Pharmacogenomics, the study of genetic factors underlying variation in drug response, is a modern term for pharmacogenetics. Pharmacogenomics involves the recognition that more than one genetic variant may contribute to variation in drug response. Historically, the field of study began with observations of severe adverse drug reactions in certain individuals, who were found to harbor genetic variants in drug metabolizing enzymes [6].

3. Genes related to hypertension

Genes involved in the phenotypes of various pathologies, such as diabetes, atherosclerosis and hyperlipidemia, are clinically implicated in arterial hypertension. They encode proteins that influence some of the pathophysiological determinants of hypertension: myocardial contractility, blood volume and vascular resistance [3]. (Table 3)

None of the genes involved in BP regulation is conferred a determinant value, nor do they act in isolation; the sum of the risk alleles or how they are combined will influence the final phenotype.

All cases in which a single gene is responsible for AH are rare. This etiology should be suspected when the genealogy shows a defined pattern of inheritance, either dominant or recessive; it is usually severe AH and often of early onset, even in childhood or adolescence.

Among them are variants in:

- The angiotensinogen gene located on chromosome 1, active especially in liver cells, is responsible for angiotensinogen synthesis. The gene has a certain nucleotide sequence, but there are some variants of this sequence present in a variable percentage of the population and which result in a polypeptide slightly different from the most common; the most common variants are *M235T* and *T174M*, which means that in the case of *M235T*, in amino acid 235, methionine has been replaced by threonine and in the second case, *T174M*, in amino acid 174, methionine is found instead of threonine. Both variants are found in different proportions in various populations and are associated with a higher frequency of AH in those who carry them, especially for those who are homozygous for one of these variants or those who carry one or two alleles that combine both variants [3].
- The gene encoding renin is located on chromosome 1, in a locus different from the previous gene. It exerts its action in the juxtaglomerular cells of the kidney, responsible for secreting renin, which, by cleaving angiotensinogen to form angiotensin I, initiates the cascade of events of the RAAS, culminating in the formation of aldosterone with the consequent vasoconstriction and elevation of BP [3].
- The renin receptor gene, called *ATP6AP2*, is located on the X chromosome. Renin bound to its receptor induces a rate of angiotensin I formation four times greater than that induced by soluble renin. At the same time, renin stimulation activates the *ERK1* (*MAPK3*) and *ERK2* (*MAPK1*) genes, which are related to obesity and cardiac hypertrophy, among other things [3].
- The *ACE* gene, which converts angiotensin I into the active peptide angiotensin II, has two possible variants: I (insertion) or D (deletion), referring to the presence or absence of a 287 base pair fragment in intron 16 of the gene. The presence of the D allele is associated with higher plasma ACE activity, especially in DD homozygotes, and also with a lower hypertensive response to metoprolol compared to homozygotes for the allele with insertion (genotype II) in certain populations. It is not clear how this variant acts since it is located in an intron and is not transcribed; therefore, the resulting polypeptide should not be different in each case. Angiotensin II interacts with two types of cell surface receptors, type 1 and type 2, encoded by the *AGTR1* and *AGTR2* genes, of which the former is the most important since its increased expression induces myocardial hypertrophy and hypertension; from the pharmacological point of view, receptor 1 antagonists, such as losartan, are effective in the treatment of angiotensin II-dependent hypertension [3].
- In the event of a case of the aldosterone synthase gene (*CYP11B2*) has the -344C/T variant, it confers an increased risk of cerebral infarction and hypertension [3].
- Variants in the *HSD3B1* and *HSD3B2* genes, which encode enzymes necessary for the synthesis of steroid hormones, influence the risk of hypertension [3].
- The *ADD1* gene, located on chromosome 4p, encodes a protein called adducin 1, which is found in the membrane cytoskeleton and promotes binding between spectrin and actin. Due to its interaction between actin and spectrin filaments, it has an important role in membrane architecture and, potentially, in the activity of certain channels, in particular Na-K-Cl cotransport and Na-K-ATPase. The G460W variant of the *adducin1* gene is more frequent in hypertensives than in normotensives, and seems to predispose to a particular sensitivity to salt and hypertension [3].

3.1. Familial hyperaldosteronism type 1

Also called glucocorticoid-remediable hyperaldosteronism (GRA) or glucocorticoid-suppressible hyperaldosteronism (GSH), it is caused by a genetic point defect, the fusion of two contiguous genes, *CYP11B2* and *CYP11B1*, located on the long arm of chromosome 8. This hybrid gene is responsible for a picture of hyperaldosteronism hypertension that can be successfully treated with dexamethasone. It is a very rare form of primary hyperaldosteronism that usually manifests

in adulthood. Inheritance is autosomal dominant, although with incomplete penetrance, some carriers do not manifest the phenotype [3].

3.2. Familial hyperaldosteronism type 2

It has the same symptoms as type 1, but does not respond to treatment with dexamethasone. The causative gene is not yet known, but linkage studies indicate that it is located on the short arm of chromosome 7, region 7p22 [3].

Apparent mineralocorticoid excess syndrome (AME) caused by a mutation of the *HD11B2* gene encoding the enzyme cortisol 11-betacetoreductase, which converts cortisol to cortisone. When the enzyme is missing, blockage of this pathway occurs, causing a great elevation of cortisol, which, due to its abundance, replaces aldosterone in its function of regulating the mineralocorticoid receptor, which is overstimulated. The patient has all the symptoms of hyperaldosteronism, including hypertension and hypokalemia, which begin in infancy; treatment with dexamethasone to regulate cortisol secretion is effective. Inheritance is autosomal recessive [3].

4. Liddle's syndrome

Also called pseudoaldosteronism, it presents symptoms similar to those of the syndrome of apparent mineralocorticoid excess (AME) but without an effective response to dexamethasone. There is hypertension with hypokalemia due to dysfunction of the renal epithelial sodium channel, a failure caused by mutations of the genes encoding the beta or gamma subunits of this channel (*SCNN1B* and *SCNN1G*), both located on chromosomal locus 16p13–12, and for which there is a possibility of molecular diagnosis. Other genes that interact with those mentioned and whose mutations also cause Liddle syndrome are *NEDD4*, *NEDD4L* and *NR3C2*. The inheritance of this syndrome is autosomal dominant [3].

5. Pharmacodynamics of antihypertensives

Human Genome Sequencing seeks to understand and diagnose pathologies, as well as to create more effective therapeutic methods with minimal adverse effects. In the case of hypertension, there are certain linked genes that interact with the antihypertensive drugs to obtain a treatment response, such as a decrease of BP, as well as an increase of adverse effects. (Table 4)

5.1. Diuretics

NEDD4L is a neural precursor essential for the maintenance of proper sodium reabsorption. It has ADD1 a cytoskeleton protein in charge of ion transport regulation, and it has been observed that hypertensive patients with *ADD1* and *NEED4L* genes treated with hydrochlorothiazide (first-choice diuretic drug belonging to the thiazide group) presented a fall in BP, since it inhibits the Na+/Cl- cotransporter and decreases sodium reabsorption in the renal tubule [15].

5.2. Angiotensin receptor blocker

In a study angiotensin receptor blocker and hypertension were associated with the variant of the *FUT4* gene, and it was observed that with candesartan therapy there was a decrease in blood pressure levels, but it's not clear what's the interaction between the gene and the drug [15].

5.3. Beta-adrenergic blockers

Beta-adrenergic blockers have Federal Drug Administration (FDA) approval to treat patients with systemic hypertension. Metoprolol, propranolol, and carvedilol have been proven effective in the treatment of HTN and can be used once daily. Labetalol is the only beta-blocker indicated for parenteral management of HTN emergencies and for treatment of intraoperative and postoperative HTN [26].

Combining beta-blockers with diuretic drugs has been shown to have better antihypertensive effects, such as HCTZ, chlorthalidone and chlorothiazide, as well as combination with calcium channel blockers like hydralazine, minoxidil and dihydropyridine [26].

Alpha-adrenergic blockers lower DBP in hypertensive patients, an alpha-adrenergic blocker, doxazosin have an important role lowering glucose and lipids aside from its BP lowering effects, and combined with an angiotensin-converting enzyme inhibitor and a calcium-channel blocker have superiority over a thiazide diuretic in the treatment of hypertension.

6. Centrally active hypertensive drugs

Clonidine activates a specific receptor in the body called alfa-2A adrenergic receptor, and can lower blood pressure in hypertensive patients who have specific genetic variations in TT genotype of a gene called *GNB3 rs5433*. The *GNB3* gene is involved in guanine nucleotide-binding proteins and is linked to various clinical conditions, including essential hypertension. The researcher examined that alfa-2A adrenergic receptors are plentifully present in a specific area of the brain called the gigantocellular depressor area (GiDA) located within the reticular formation [15].

6.1. Angiotensin Converting Enzyme (ACE)

The renin-angiotensin-aldosterone system (RAS) is a hormone-independent paracrine system that plays an increasingly prominent role in hypertension and renal disease [16].

Angiotensin-converting enzyme (ACE), a ubiquitous metalloprotease, emerges as a molecular entity present in its two main isoforms: ACE-1 (found in the vascular endothelium, consisting of two catalytic domains linked by an extracellular segment) and ACE-2 (with a role in the regulation of the cardiovascular system), both of transcendental importance in cardiovascular physiology and fluid homeostasis. Their central function lies in the conversion of angiotensin I, an inactive peptide, into angiotensin II, a bioactive hormone that triggers key physiological responses.

ACE catalyzes the cleavage of a peptide from angiotensin I, thereby releasing angiotensin II, which has vasoconstrictive properties and stimulates the release of aldosterone. This process directly influences the regulation of vascular tone and fluid homeostasis by increasing sodium and water retention.

The clinical importance of ACE is manifested in its relationship to arterial hypertension, in which pharmacological inhibition of this enzyme has become a therapeutic cornerstone. ACE inhibitors have demonstrated their efficacy in mitigating the formation of angiotensin II, inducing vasodilatation and reducing blood pressure.

6.2. Angiotensin-converting enzyme inhibitors

Angiotensinogen is expressed in the liver and is encoded by the *AGT* gene, located on chromosome 1q42-q43. In the renin-angiotensin pathway, the *AGT* gene is one of the important genes associated with the pathophysiology of hypertension [15].

A single precursor of angiotensin peptides, angiotensinogen, secreted by hepatocytes, is converted to angiotensin I (decapeptide) by renin. Membrane-bound ACE cleaves angiotensin I decapeptide to generate angiotensin II octapeptide. The AGT gene encodes angiotensinogen, and overexpression of the *AGT* gene (*KAP-AGT* transgene) in animal models and variant of the ACE gene in hypertensive patients showed an increase in circulating angiotensinogen and plasma ACE. This leads to increased angiotensin II generation and sodium reabsorption. Because ACE inhibitors block the conversion of angiotensin I to angiotensin II by inhibiting ACE, ACE inhibitors could interact with the ACE gene variant and reduce blood pressure [15].

6.3. Calcium Channel Blockers

The voltage-dependent calcium channel alpha-1 C subunit gene (*CACNA1C*) encodes the α1c subunit of the L-type calcium channel (dihydropyridine or DHP channel). This is one of the critical binding sites for calcium channel blockers (CCB).

The *CACNA1C* gene encodes the α1c subunit of the L-type calcium channel. These voltage-dependent Ca2+ channels mediate Ca2+ entry into excitable cells, helping regulate blood pressure [15].

L-type Ca2+ channels (Ca_L), voltage-dependent K+ channels (K_V), and high-conductance voltage and Ca^{2+}-sensitive K+ channels (BK_{Ca}) are voltage-sensitive channels. These channels play a crucial role in regulating smooth muscle tone in arteries. Evidence suggested that positive regulation of L-type Ca channels (overexpression of $_{1c}$) as well as loss of Kv channels (voltage-activated potassium channels) results in channel opening and causes depolarization. This results in increased voltage-dependent Ca2+ influx in arteries, leading to vasoconstriction and high blood pressure. CCBs bind to the α1 subunit and interfere with the voltage-dependent channel cycle. Phenylalkylamines bind to the open and inactivated state with high affinity and reduce incoming Ca2+ currents through L-type Ca2+ channels (LTCC), mainly Cav (voltage-activated Ca channels) [15].

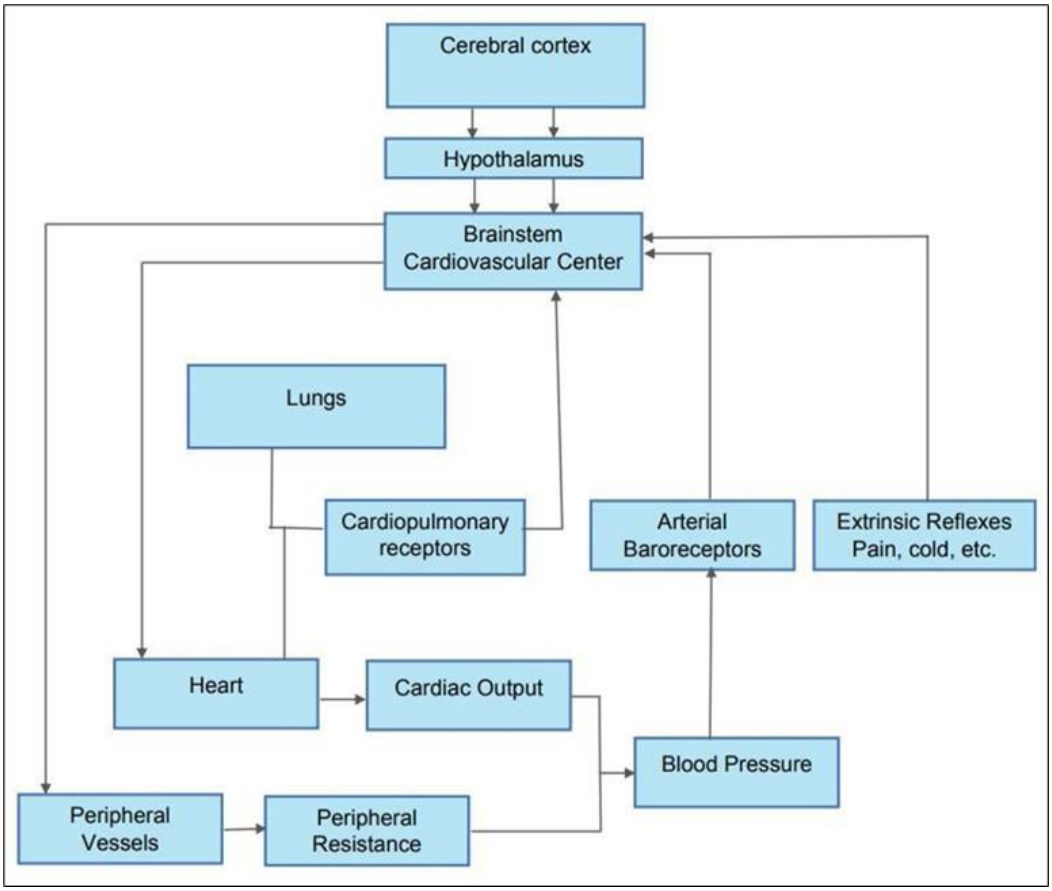

Figure 1 Short-team regulation of blood pressure by nervous mechanisms (taken from femandez-tresguerres,JA)[2]

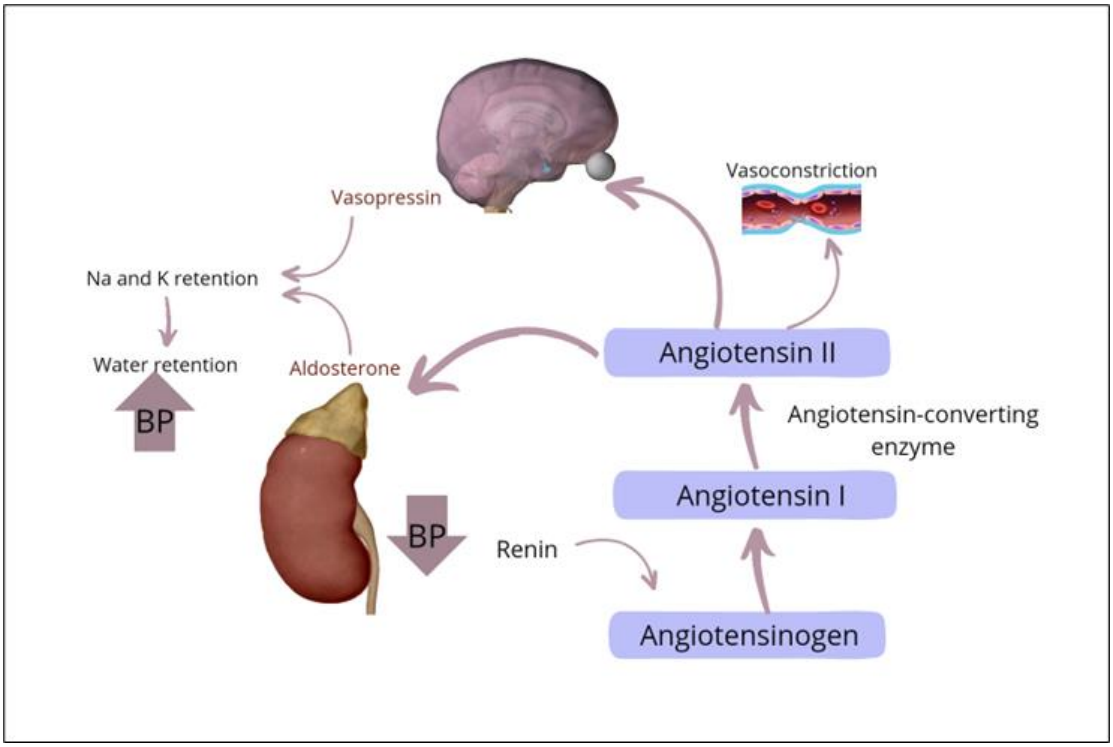

Figure 2 Renin-angiotensin-aldosteron-system

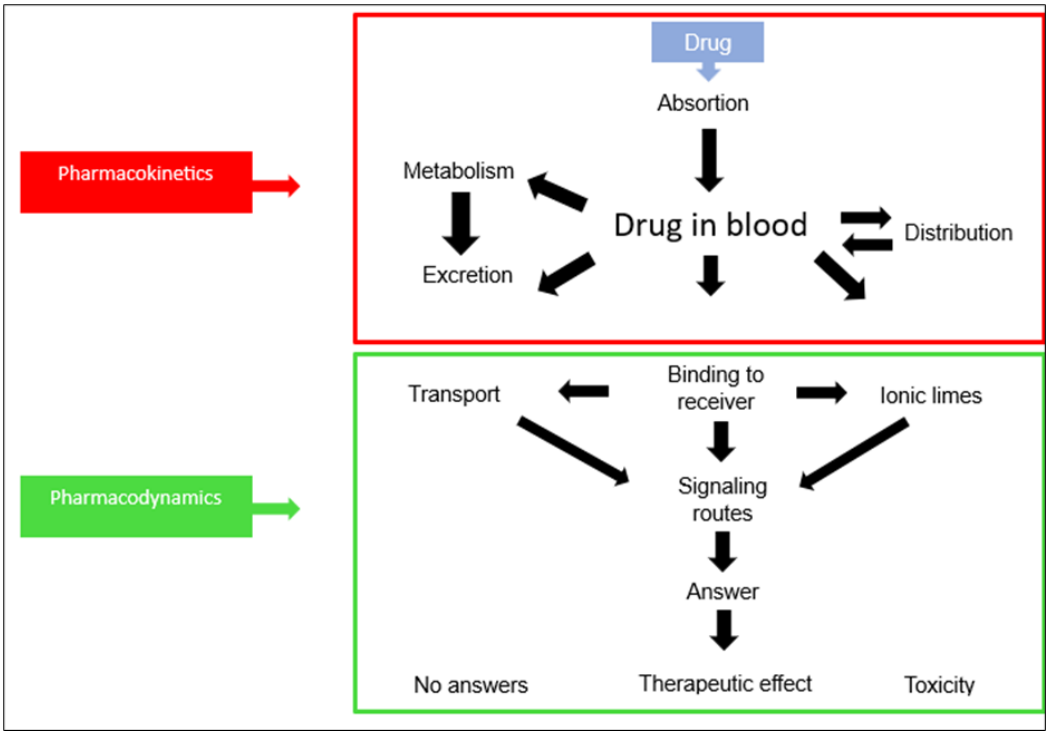

Figure 3 Pharmacokinetics and pharmacodynamics (8)

Table 1 Variation of blood pressure throughout life(4)

Age (years)	Men (mm Hg)	Women (mm Hg)
1	96/66	95/65
5	92/62	92/62
10	103/69	103/70
20-29	123/76	116/72
30-39	126/79	120/75
40-49	129/81	127/80
50-59	135/83	137/84
60-69	142/85	144/85
70-79	145/82	159/85
80+	146/82	157/83

Table 2 Some genes related to essential hypertension (3)

Symbol	Observation	Locus
AGT	Angiotensinogen	1q42
REN	Renin	1q32
AGTR1	Angiotensin receptor 1	3q21-25
AGTR2	Angiotensin receptor 2	Xq22

RCT (ACE)	Angiotensin converting enzyme	17q23
ATP6AAP2	renin receptor	Xp11
ERK1 (MAPK3)	Renin-activated protein kinase	16p11
ERK2 (MAPK1)	Renin-activated protein kinase	22q11
CYP11B2	Aldosterone synthase	8q21
NEDD4L	Ubiquitin ligase	18q21
ECE1	endothelin-converting enzyme	1p36
ATP1B1	ATPase B1-Na+/K+ transport	1q22
ADD1	Aducina 1 alpha	4p16

Table 3 Genes related to essential hypetension

Symbol	Observations	Locus
AGT	Angiotensinogen	1q42
REN	Renin	1q32
AGTR1	Angiotensin receptor 1	3q21-25
AGTR2	Angiotensin receptor 2	Xq22
ECA (ACE)	Angiotensin-converting enzyme	17q23
ATP6AP2	Renin receptor	Xp11
ERK1(MAPK3)	Renin-activated protein kinase	16p11
ERK2(MAPK1)	Renin-activated protein kinase	22q11
CYP11B2	Aldosterone synthase	8q21
NEDD4L	Ubiquitin ligase	18q21
ECE1	Endothelin-converting enzyme	1p36
ATP1B1	ATPaseB1- Na+/K+ Transport	1q22
ADD1	Alpha-adducin 1	4p16

Table 4 Major therapeutic groups with antihypertensive action and their mechanisms of action (12,13)

Therapeutic Group	**Mechanism of Action**	**Examples**
Angiotensin-Converting Enzyme Inhibitors (IECA)	Inhibition of ECA, responsible for the conversion of angiotensin I to angiotensin II.	Enalapril Lisinopril Captopril
Angiotensin II Receptor Antagonists (ARA-II)	Blocking of the angiotensin II receptor, thereby reducing its effects.	Valsartan Losartan Olmesartan Irbesartan
Renin Inhibitors	Inhibition of renin, responsible for the conversion of angiotensinogen to angiotensin.	Aliskiren
B-Blockers	Blocking of type 1 ß-adrenergic receptors, leading to a decrease in contractile force and heart rate. They also act on the production of catecholamines and the release of	Atenolol Bisoprolol Carvedilol

	renin. Additionally, some have a1 antagonist action, causing a direct vasodilatory effect.	
Calcium Channel Blockers	Blocking of calcium entry through L-type channels, resulting in vasodilation. Non-dihydropyridine compounds also reduce contractile force and heart rate.	Dihydropyridines: Amlodipine, Nifedipine, Nicardipine Non-dihydropyridines: Verapamil, Diltiazem
Thiazide Diuretics	Increased renal sodium excretion, reducing plasma volume. In the long term, they decrease peripheral resistance.	Hydrochlorothiazide Chlorothiazide Chlortalidone
Potassium-Sparing Diuretics	Increased renal sodium excretion by inhibiting sodium channels or antagonizing aldosterone receptors.	Spironolactone Eplerenone Amiloride
Loop Diuretics	Increased renal sodium excretion, reducing plasma volume.	Furosemide Torsemide
Others A1 Adrenergic Blockers Central Hypotensive Agents Potassium Channel Agonists NO Mediated Vasodilators	Blocking of alpha-1 adrenergic receptors in blood vessels, causing vasodilation. Activation of central alpha-2 receptors and/or imidazoline receptors, reducing sympathetic activity. Opening of potassium channels, promoting cell hyperpolarization and vasodilation. Vasodilation produced by the release of nitric oxide.	Doxazosin, prazosin, terazosin Clonidine, methyldopa, moxonidine Minoxidil Hydralazine, nitroprusside

Abbreviations

AH: arterial hypertension, HBP: high blood pressure, BP: blood pressure, RAAS: Renin-angiotensin-aldosterone system, ACE: Angiotensin converting enzyme, CCB: Calcium channel blockers, AME: syndrome of apparent mineralocorticoid excess.

7. Conclusion

The integration of pharmacogenetics into the treatment of hypertension offers a promising prospect for the medicine of the future. By understanding how genetic factors influence individual drug response, physicians can tailor treatments in a more precise and personalized manner. This deeper understanding of patients' genetic profile allows maximizing drug efficacy while minimizing adverse reactions; likewise, the importance of pharmacogenetics in the treatment of hypertension lies in its ability to generate better therapeutic outcomes and reduce the time needed to find the optimal drug combination. This patient-centered approach not only improves the quality of life of individuals, but can also reduce the costs associated with the treatment of hypertension and other chronic diseases.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Bravo LGB. Farmacología del Losartán y otros antihipertensivos. RECIAMUC [Internet]. 2022 Mar 3 [cited 2022 Apr 10]; 6(1):332–40. Available from: https://www.reciamuc.com/index.php/RECIAMUC/article/view/795

[2] Shahin MH, Johnson JA. Mechanisms and pharmacogenetic signals underlying thiazide diuretic blood pressure response. Current Opinion in Pharmacology 2016, 27:31-37.

[3] Quiroga de Michelena María Isabel. Hipertensión arterial: aspectos genéticos. An. Fac. med. [Internet]. 2010 Dic; 71(4): 231-235. Disponible en: http://www.scielo.org.pe/scielo.php?script=sci_arttext&pid=S1025-55832010000400004&lng=es

[4] Fernández-Tresguerres, JA. Fisiología humana. 4ª Edición. Madrid: McGraw-Hill; 2010.

[5] Adams M, Leland Norman Holland, Paula Manuel Bostwick. Farmacología para enfermería: un enfoque fisiopatológico. Madrid: Pearson Prentice Hall; 2009.

[6] Katzung BG. Farmacología básica y clínica. 14th ed. México, D.F. Etc.: Mcgraw Hill, Cop; 2019.

[7] Bakris G. High Blood Pressure - Heart and Blood Vessel Disorders [Internet]. MSD Manual Consumer Version. 2022. Available from: https://www.msdmanuals.com/home/heart-and-blood-vessel-disorders/high-blood-pressure/high-blood-pressure

[8] De U, Facultad S, Farmacia D. RESPUESTA TERAPÉUTICA JOSÉ MIGUEL CANAL PÉREZ [Internet]. [cited 2023 Sept 20]. Available from:https://idus.us.es/bitstream/handle/11441/64776/CANAL%20P%C3%89REZ%2C%20JOS%C3%89%20MIGUEL.pdf?sequence=1&isAllowed=y#:~:text=Uno%20de%20los%20factores%20influyentes

[9] Turnpenny PD, Ellard S. Emery's elements of medical genetics. Philadelphia, Pa: Churchill Livingstone/Elsevier; 2017.

[10] Adams M, Leland Norman Holland, Paula Manuel Bostwick. Farmacología para enfermería: un enfoque fisiopatológico. Madrid: Pearson Prentice Hall; 2009.

[11] Turner AJ, Nalivaeva NN. Angiotensin-converting enzyme 2 (ACE2): Two decades of revelations and re-evaluation. Peptides. 2022 May;151:170766.

[12] Quiñones L, Roco A, Miranda C. Farmacogenómica: aplicaciones cardiovasculares. Rev. Med. Clin Condes 2015; 26(2) 198-209.

[13] Flórez J, Armijo J, Mediavilla A. Farmacología humana. 6ª Edición. Barcelona: Elsevier Masson; 2014.

[14] Turner ST, Schwartz GL, Chapman AB, Hall WD, Boerwinkle E. Antihypertensive Pharmacogenetics: getting the right drug into the right patient. J Hypertens. 2001 Jan; 19(1):1-11. doi: 10.1097/00004872-200101000-00001. PMID: 11204288.

[15] Rahman, Farhana, et al. "Current Concepts and Molecular Mechanisms in Pharmacogenetics of Essential Hypertension." Indian Journal of Pharmacology, vol. 53, no. 4, 1 July 2021, pp. 301–309, europepmc.org/article/MED/34414909, https://doi.org/10.4103/ijp.ijp_593_19. Accessed 14 Dec. 2022.

[16] Culver S, Li C, Siragy HM. Intrarenal Angiotensin-Converting Enzyme: the Old and the New. Current Hypertension Reports. 2017 Sep 19;19(10).

[17] Lara O Karlena C, Mendible Juan C, Ramírez Carlos D, Hung Alida. Polimorfismos en el Promotor del Gen del Angiotensinógeno (AGT) y su relación con la miocardiopatía chagásica crónica en pacientes venezolanos. INHRR [Internet]. 2004 Jul [citado 2023 Oct 23] ; 35(2): 14-19. Disponible en: http://ve.scielo.org/scielo.php?script=sci_arttext&pid=S0798-04772004000200004&lng=es.

[18] Saseen JJ. Pharmacologic Management of Hypertension. En: DiPiro JT. Pharmacotherapy: a pathophysiologic approach. 8th edition. New York: McGraw-Hill Medical; 2011. p. 474-489.

[19] Rodríguez Arcas MJ, García-Jiménez E, Martínez-Martínez F, Conesa-Zamora P. Papel del citocromo P450 en la farmacocinética y en la farmacogenética de los fármacos antihipertensivos. Farm Hosp. 2011; 35(2):84-92.

[20] Arikkath J, Chen C-C, Ahern C, Allamand V et al. γ1 subunit interactions within the skeletal muscle L-type voltage-gated calcium channels. The Journal of Biological Chemistry, 2003, 278:1212-1219.

[21] Karki R, Pandya D, Elston RC, Ferlini C. Defining "mutation" and "polymorphism" in the era of personal genomics. BMC Med Genomics 2015; 8:37.

[22] Danilov SM, Tovsky SI, Schwartz DE, Dull RO. ACE Phenotyping as a guide toward personalized therapy with ACE inhibitors. Journal of Cardiovascular Pharmacology and Therapeutics 2017, Vol. 22(4) 374-386.

[23] Shahin MH, Johnson JA. Mechanisms and pharmacogenetic signals underlying thiazide diuretic blood pressure response. Current Opinion in Pharmacology, 2016, 27:31-37.

[24] Mills, KT et al. Global Disparities of hypertension Prevalence and control: a systematic analysis of Population-Based studies From 90 countries. Circulation. 2016; 134:441–450.

[25] Organización Mundial de la Salud. Información general sobre la hipertensión en El Mundo. 2013. Número de documento: WHO/DCO/WHD/2013.2. Whelton PK et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/ NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017.

[26] MacLaughlin EJ, Saseen JJ. Hipertensión. En: DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. DiPiro editores. Farmacoterapia: un enfoque fisiopatológico, 11e. McGraw Hill; 2020. Consultado el 15 de septiembre de 2023. https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577§ionid=220356112

[27] Borobia AM, Dapia I, Tong HY, Arias P, Muñoz M, Tenorio J, et al. Clinical Implementation of Pharmacogenetic Testing in a Hospital of the Spanish National Health System: Strategy and Experience Over 3 Years. Clinical and Translational Science [Internet]. 2018 Mar 1;11(2):189–99. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5866958/

[28] Frishman WH. Beta-adrenergic receptor blockers in hypertension: Alive and well. Prog Cardiovasc Dis [Internet]. 2016;59(3):247–52. Disponible en: http://dx.doi.org/10.1016/j.pcad.2016.10.005

[29] Lara O Karlena C, Mendible Juan C, Ramírez Carlos D, Hung Alida. Polimorfismos en el Promotor del Gen del Angiotensinógeno (AGT) y su relación con la miocardiopatía chagásica crónica en pacientes venezolanos. INHRR [Internet]. 2004 Jul [citado 2023 Oct 23] ; 35(2): 14-19. Disponible en: http://ve.scielo.org/scielo.php?script=sci_arttext&pid=S0798-04772004000200004&lng=es