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КРАТКИЙ ОБЗОР ИСТОРИИ РАЗВИТИЯ ФАРМАКОЛОГИЧЕСКОЙ АНТИГИПЕРТЕНЗИВНОЙ ТЕРАПИИ

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A Brief Overview of The History of The Development of Pharmacological Antihypertensive Therapy

Резюме

На протяжении многих десятилетий сердечно-сосудистые заболевания занимают лидирующую позицию в структуре смертности во всем мире. Имеются данные, что общее число сердечно-сосудистых заболеваний удвоилось за последние 30 лет, а число смертей от них выросло на 65 % за это же время. Вместе с тем увеличивающаяся распространенность артериальной гипертензии как важнейшего фактора риска сердечно-сосудистых заболеваний представляет собой глобальную проблему всемирного здравоохранения. В такой ситуации актуален вопрос антигипертензивной терапии, её качества. Сохраняется потребность в дальнейших исследованиях новых классов антигипертензивных препаратов. В статье кратко обсуждается эволюция взглядов на патогенез артериальной гипертензии, поэтапное внедрение в широкую клиническую практику препаратов, снижающих артериальное давление. Также в статье приведены новые группы препаратов и последние тенденции в лечении артериальной гипертензии.

Ключевые слова: *история медицины, кардиология, гипертоническая болезнь, антигипертензивные препараты*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

For many decades, cardiovascular diseases have been the leading cause of death worldwide. There is evidence that the total number of cardiovascular diseases has doubled over the past 30 years, and the number of deaths from them has steadily increased by 65 % over the same time. At the same time, the increasing prevalence of arterial hypertension as the most important risk factor for cardiovascular diseases is a global problem for world health. In this situation, the issue of antihypertensive therapy and its quality is relevant. There is still a need for further research into new classes of antihypertensive drugs. The article briefly discusses the evolution of views on the pathogenesis of arterial hypertension, the gradual introduction of drugs that lower blood pressure into widespread clinical practice. The article also presents new groups of drugs and the latest trends in the treatment of arterial hypertension.

Key words: *history of medicine, cardiology, hypertension, antihypertensive drugs*

Conflict of interests
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EH — essential hypertension, BP — blood pressure, BBs — beta-blockers, CCBs — calcium channel blockers, DBP — diastolic blood pressure, ACEIs — angiotensin-converting enzyme inhibitors, siRNA — small interfering RNA, RAAS — renin-angiotensin-aldosterone system, RH — resistant hypertension, SBP — systolic blood pressure, CVDs — cardiovascular diseases, CHF — chronic heart failure

Introduction

When no blood pressure (BP) measurement devices existed, its elevation was suspected based on indirect signs: cardiomegaly, pulse tension, second cardiac tone accent over the aorta. For the first time BP was measured by an English physician S. Gales in 1733: during the experiment, he determined the height of the blood column in a glass tube inserted into the carotid artery of the horse. The first accurate BP evaluation in a human was arranged invasively by the surgeon Febvre in 1856 [1]. In 1905, the Russian surgeon N.S. Korotkov proposed an auscultation method of BP measurement; this technique has been used globally for over 100 years thanks to its simplicity and comfort.

Such studies have laid a foundation for analyzing pathological BP alterations. Currently we know about a mosaic theory of essential hypertension pathogenesis as a complex of various system effects and BP regulation pathways, which explains a constant search for efficient methods of affecting the maximum number of pathogenetic mechanisms by analyzing and synthesizing new drugs from various groups, dose optimization, and drug combinations. This awareness was not always present: the medical and scientific society has cleared a long way to arrive at the current treatment level. Starting from the 20th century, the development of hypotensive therapy may be analyzed using a time scale illustrating the rate with which new hypotensive agents become available in the clinical practice of modern physicians (**Figure 1**), while changes in pharmacotherapeutic BP lowering strategies with time are presented in **Table 1**.

The concept of normal BP level has also been altered for quite a long time. Currently, a trend to strict BP control prevails. Based on the opinions of American Heart Association and American College of Cardiology, the modern target BP level for adults with confirmed hypertension is SPB <130 mm Hg, DBP <80 mm Hg [2]; however, in 1960s BP was considered elevated when reaching values over 160/110 mm Hg, while the medical society debated whether one should decrease elevated BP, as the latter one was considered an inevitable and, thus, significant component of the body aging process.

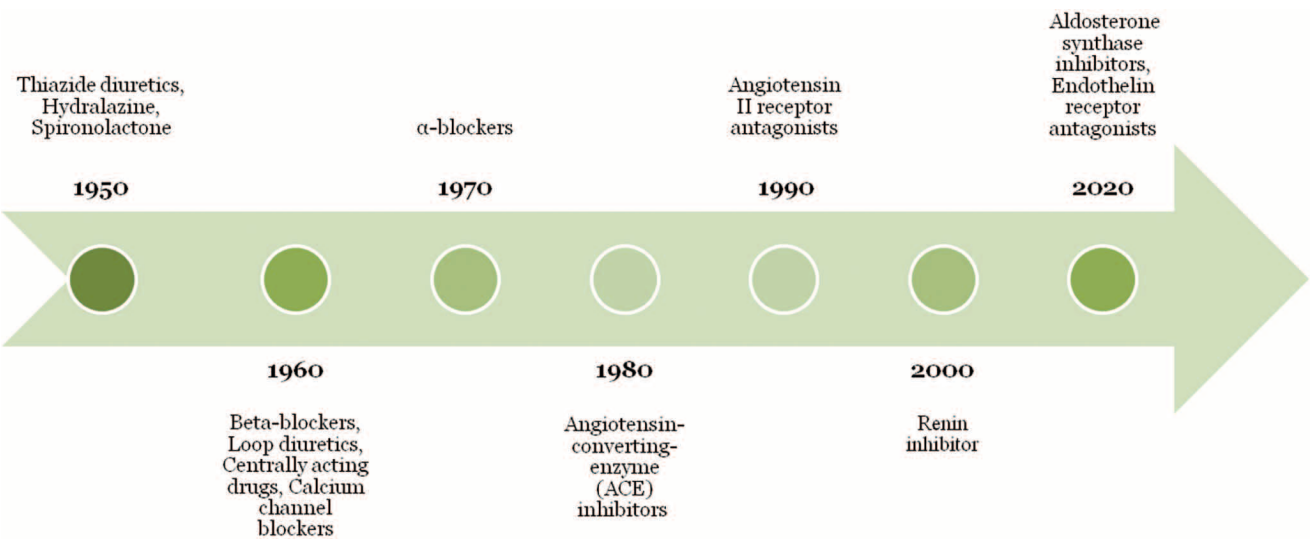

Figure 1. *Chronology of the introduction of different groups of antihypertensive drugs into clinical practice for the first time*

Table 1. Pharmacotherapeutic strategies for the treatment of arterial hypertension in a historical context

Stage	Means	Features
Antiquity and the Middle Ages	Bloodletting, herbal and animal remedies, dietary changes	Low efficiency, health hazard
Beginning of the 20th century	Nitrates, sodium nitroprusside, mercury diuretics, sedatives	Large number of side effects, toxicity, poorly predicted hypotensive effect
Mid 20th century	Ganglionic blockers, α-blockers and centrally acting drugs, acetazolamide, thiazide and loop diuretics, first beta-blockers and calcium channel blockers	The search for more effective and safer means continues; many representatives of these groups have remained relevant to this day
The turn of the 20th-21st century	ACE inhibitors, Angiotensin II receptor antagonists, latest generations of beta-blockers and calcium channel blockers, renin inhibitor	Greater efficacy and safety; significant reduction in mortality from cardiovascular diseases; accumulation of scientific research data
Modernity	Active use of combinations of antihypertensive drugs from different groups	Emphasis on an individual approach to the treatment of high blood pressure, on low doses of drugs used, on the impact on various links in the pathogenesis of hypertension; continued search for means in accordance with scientific discoveries and the development of pharmacology

Pharmacological Agents Used for Decreasing Blood Pressure

Depressive (sedative) drugs

At the beginning of the 20th century, understanding a significant role of sympathetic regulation in the pathogenesis of essential hypertension (EH) led to the search for methods to affect it as one of the treatment principles. Significant attention was paid to the emotional condition of patients with hypertension. The founder of the Russian electrocardiography L.I. Fogelson wrote: "Medications should be used to decrease the nervous system excitability and to decrease the tone of peripheral arteries. Bromides and valerian drugs, luminal act well as general tranquilizers, decreasing the excitability of the autonomous nervous system centers" [3]. In his article "Hypertension (experience of the analysis of its origin)", D.D. Pletnev, one of the teachers of A.L. Myasnikov, stated that "warm "indifferent" baths, bromides, valerian drugs are beneficial" in the treatment of essential hypertension [4]. In his monumental monograph "Essential hypertension", G.F. Lang also underlined the role of luminal in "decreasing the excitability of both autonomous hypothalamic centers and the brain cortex", as well as mentioning the barbituric acid compound in the treatment of essential hypertension with artificial intermittent or continuous sleeping [5].

Drugs based on natural agents

The role of vascular tone as one of the pathogenetic aspects in EH urged to consider those substances that were known for a long time to affect the vascular tone. Thus, plant extracts containing poisonous alkaloids and causing the vascular collapse among other effects, have been known from ancient times. Considering plants as a ready-to-use drug product, one cannot avoid alkaloid-containing drugs, that became the most popular in the middle of the 20th century due to the unsatisfactory prior therapy and significant progress in the chemical industry. Salsoline was a vasodilating agent used in essential hypertension ("early disease with unstable blood pressure"). Salsoline was an isoquinoline derivative, an alkaloid derived from aerial parts of the Asian plant Richter's saltwort. Due to the emergence of more efficient agents, by 1981 the USSR Ministry of Health excluded salsoline and its combinations from the drug product nomenclature. A bright representative of plant-derived alkaloids, reserpine (a sympatholytic agent isolated from Rauwalfia serpentina), was synthesized artificially by R.B. Woodword in 1956 [6]. Reserpine had multiple adverse effects, including angina worsening. A Soviet biochemist V.A. Dadali developed a drug product raunatine based on the same Rauwalfia alkaloids — its sedative effects were less significant than in reserpine, while it was not inferior in hypotensive effects. An opium alkaloid papaverine known for approximately two centuries was also popular in the 20th century as a hypotensive agent, just like another spasmolytic drug bendazole. Up till the present time, bendazole, papaverine and their combination can be found on the pharmaceutical market. These drugs have not been supported with clinical evidence, but are characterized by a large number of adverse effects, including decreased myocardial contractility and cardiac output, delayed cardiac conductivity (even with complete AV-block), and significant autonomous disorders. Ergotamine isolated in 1918 from the mixture of ergot (parasitic fungus) alkaloids can be rightly considered a precursor of alpha-blockers [7].

Diuretics

Pathological effects of fluid excess in EH pathogenesis led to the attempts of using diuretics. Since ancient times, a search of agents to relieve edema continued; based on empiric observations, edema relief also led to BP decrease. The following substances were used in previous centuries with diuretic purposes: mineral mercury compounds; sea onion infusion; rockberry (bear berry) leaves containing an arbutine glycoside with diuretic effects. Thiazide diuretics were created only by the end of 1950s, but they have proven their high efficacy specifically in the treatment of EH. The largest ALLHAT hypotensive treatment trial (42,000 patients) arranged in more than 600 North American hospital for 8 years, starting in 1994, demonstrated a high efficacy of a thiazide-like diuretic chlorthalidone in the prevention of cardiovascular complications, which was not inferior to angiotensin-converting enzyme inhibitors (ACEIs) and calcium channel blockers (CCBs) [8].

Central hypotensive drugs

The effects of neural regulation in the structure of EH pathogenesis often led to the attempts of analyzing the effects of a specific substance by inhibition or mimetic effects on specific receptors, with subsequent BP alteration directly or indirectly. Thus, clonidin, an imidazole derivative (centrally acting drug), was developed in 1960s as a decongestant; however, its hypotensive properties were almost always observed. As a hypotensive drug, clonidine was priorly used for several decades in the USSR and other countries. The adverse sedative effect of clonidine caused by the activation of α2-adrenoceptors located in the locus ceruleus initiated the development of drugs with more selective effects. Currently second-generation selective agonists of imidazole I1 receptors (moxonidine, rilmenidine) are widely available — these don't have adverse effects of clonidine, but rather provide pleiotropic features (decreased insulin resistance, lipid metabolism regulation, neuroprotection, effects on inflammation and cellular proliferation processes, etc.) [9]. The originator of this group, methyldopa, is included into the List of Vital and Essential Drugs (as of 2025), being one of a few agents approved for use in pregnancy.

Beta-blockers

The physiological effects of adrenal gland extracts on the cardiovascular system were first described at the end of the 19th century. Meanwhile, in 1898 John Jacob Abel obtained a crystalline substance from these extracts with the ability to increase BP; he called it epinephrine ("above the kidney") [10]. Several decades of studies enabled to prove the effects of catecholamines on myocardium and to discover adrenoceptors. 60 years later, in 1958, the first beta-blocker (BB) dichloroisoproterenol was synthesized [11], although it was refuted due to significant intrinsic sympathomimetic activity. At the beginning of 1960s, a group of British investigators managed to synthesize propranolol. In 1964, after the publication in The Lancet, propranolol became the first-in-the-world BB to be successfully used in oral and parenteral dosage forms in clinical practice [12]. Practolol was the first cardioselective drug synthesized at the end of 1960s, but it was discontinued due to adverse effects (sclerosing peritonitis, pleurisy, keratoconjunctivitis). It has been noted that as the BB selectivity enhances, its effect concerning beta1-adrenoceptor blockade also increases. Selectivity is a dose-dependent feature, however the rate of adverse effects also increases with the dose. Due to this, decades were spent to search for highly selective BBs. This resulted in the synthesis of latest-generation BBs, including metoprolol, nebivolol, bisoprolol [13]. After the meta-analysis of L. Lindholm et al., BBs have lost the leading roles in EH pharmacotherapy. When comparing the effects of BBs with placebo or no treatment, no differences were observed in the myocardial infarction and mortality rate, while the relative stroke risk decreased twice; thus, BBs are administered only in the presence of additional indications [14].

Calcium channel blockers

In 1959 F. Dengel synthesized a papaverine analogue with negative inotropic and chronotropic effects. The substance was initially called iproveratril, then verapamil [15]. The drug was initially developed as a BB, but subsequently a feature of blocking the calcium ion flux via the slow transmembrane channels was discovered for this substance. In general, CCBs represent a heterogenous group of drug products. They differ in their chemical structure, pharmacokinetics, and pharmacodynamics, features of adverse effects, and contraindications to their use. Several authors call verapamil, nifedipine, and diltiazem first-generation drugs. CCBs have quickly reached stable positions in cardiology. Short-term effects of the first-generation drugs and a wide range of therapeutic plasma levels led to unstable vasodilating effects, variable BP and heart rate. Not all attempts to develop new CCBs were successful. For example, mibefradil, a representative of a new (in 1980s) selective T-type CCB subgroup, had a high hypotensive activity, but was not compatible with more than two dozens drugs metabolized by the P450 cytochrome 2D6 and 3A4 systems. Drugs accumulated in hazardous concentrations due to inhibitory mibefradil effects, causing the abdominal muscle necrosis, acute kidney injury, severe bradycardia [16]. CCBs have additional advantages (metabolic neutrality, anti-atherosclerotic,

anti-thrombotic, anti-ischemic effects, etc.). Currently the latest-generation CCB group includes such dihydropyridine derivatives as amlodipine and lercanidipine, which are successfully used in modern hypotensive therapy in Russia.

Non-standard peripheral vasodilator

Agents causing peripheral vasodilation due to direct relaxation of smooth vascular muscles have been an attractive group for a long time regarding their hypotensive effects. Pinacidil history is worth describing. This drug was not associated with other hypotensive agents used in clinical structures neither by the mechanism of action nor by the structure. Pinacidil belongs to a new (for 1980s) class of drugs called "potassium channel openers", acting via potassium efflux, hyperpolarizing cellular membranes, leading to the decreased intracellular calcium levels and finally to the relaxation of smooth vascular muscles. The problem of pinacidil was in frequent adverse effects resulting from its basic peripheral vasodilating activity, i.e. headache, edema, palpitations, tachycardia. These effects required treatment discontinuation or the addition of drugs from other groups [17].

Renin-angiotensin-aldosterone system blockers

More and more empiric evidence about the role of kidneys in BP regulation had accumulated by the beginning of the 20th century. Physicians attempted to treat elevated BP with macerated kidneys; features of renal and hepatic extracts prepared similarly were compared. Hypotensive effects were not detected in the latter ones [5]. However, additional data indicated that the significant amount of favorable results from the use of renal extracts in hypertension is explained by their pyrogenic effects [18]. Substances with doubtful purity caused inflammatory reactions and fever. In 1942 P. Korkoren et al. neutralized the pressor effects of angiotonin (hypertensin), also known today as angiotensin [19]. In the middle of 1960s S. Ferreira verified the angiotensin-converting enzyme [20]; the development of its inhibitors first led to the emergence of teprotide — a short-acting polypeptide extracted from the poison of the Brazilian snake jararacucu (with a multitude of adverse effects), but in 1977 the first ACEI captopril was synthesized and implemented into clinical practice. 1977 is considered the starting year for successful pharmacological blockade of the renin-angiotensin-aldosterone system (RAAS). In 1980 the therapeutic arsenal was enriched by enalapril — a second-generation drug and a long-acting ACEI. Saralazine was synthesized 2 years before teprotide — that was a peptide, the first representative of the angiotensin II receptor blocker (ARB) class, which development subsequently was much slower than that of ACEIs. Further non-peptide ARBs with the affinity to type 1 receptors started to be widely used in the treatment of EH, chronic heart failure (CHF), and chronic renal disease since the onset of 1990s [21]. In 2002 the arsenal of cardiologists was enriched by a new group with another RAAS-blocking mechanism: FDA approved the first oral direct renin inhibitor — aliskiren. Subsequently this drug circulation was prohibited, including in Russia. The ALTITUDE clinical trial demonstrated that the addition of aliskiren to standard RAAS-blocking therapy in patients with type 2 diabetes mellitus and a high risk of cardiovascular and renal events may be harmful [22]. RAAS blockers have become ubiquitous in clinical practice [23]. Clinical Guidelines "Essential hypertension in adults" (2024) list valsartan + sacubitril (a combination already used in the treatment of CHF) as a new hypotensive drug. This combination of an ARB decreasing RAAS hyperactivation and sacubitril (a neprilysin-blocking enzyme) provides additional BP lowering and may exhibit organoprotective properties, in particular decreased stiffness of major arteries in systolic EH and additional natriuresis [24].

Fixed combinations

Accounting for the multipathogenetic theory of EH pathogenesis, currently combined hypotensive treatment is justified with the possible physiological and pharmacological interactions between drugs from different classes, more intensive BP lowering, and better tolerability, prognosis and survival effects compared to monotherapy. The trend to low-dose combinations has been forming. It should be noted that the first fixed hypotensive drug combinations emerged in the beginning of 1960s. They were represented by various substances, including methyldopa + hydrochlorothiazide; hydrochlorothiazide + potassium-sparing diuretics; reserpine + hydralazine + hydrochlorothiazide (see above).

On the topic importance and pharmacokinetics features

Based on the evaluations of the Global Disease Burden (GBD) 2019 study that included all available data sources on the incidence, prevalence, lethality, mortality, and health hazards for the population of 204 countries and territories within the period from 1990 to 2019, the following statistical conclusions were made. Total cardiovascular disease (CVD) cases almost doubled from 271 million (95 % uncertainty interval [UI]: 257–285 millions) in 1990 to 523 million (95 % UI: 497–550 million)

in 2019, while the number of CVD deaths increased from 12.1 million (95 % UI: 11.4–12.6 million) in 1990, reaching 18.6 million (95 % UI: 17.1–19.7 million) in 2019 [25]. It is evident that the need for new hypotensive drugs is still here. Besides the issues of patient cure and compliance, some pharmacokinetic features are also typical for specific drug groups. For example, angiotensin II may form using pathways omitting the angiotensin-converting enzyme (chymases, CAGE, catepsine G, elastase, tonin), thus leading to pathological processes in organs and tissues that cannot be completely eliminated only by the ACEI administration [26].

Active trends

Lately a large number of variable studies have been devoted to the analysis of significance of small interfering RNA (siRNA). Cardiological markers and new-generation drug products based on siRNA are deemed prospective options. This drug group will be used for parenteral administration once in several months, which can significantly enhance the compliance. Zilebesiran is one of such developed drugs, which represents a siRNA inhibiting the angiotensinogen gene transcription in the liver [27].

New hypotensive drug classes were recently developed and tested among patients with resistant hypertension (RH) to be used after the inefficacy of three or more BP-lowering agents. Spironolactone has been administered recently to resolve RH, as excessive aldosterone synthesis is considered one of the RH mechanisms. Highly selective aldosterone synthase inhibitors (bacdrostat, lorundrostat) represent a new drug class. Some investigators fear that aldosterone synthase is highly similar to the enzyme initiating cortisol synthesis, and aldosterone synthase blockade may be associated with adrenal failure. However, the preclinical use of bacdrostat was associated with decreased aldosterone, but not cortisol levels [28].

An endothelin receptor blocker aprocitentan was authorized in 2024. Just like for aldosterone synthase inhibitors, RH is an indication for its use. Aprocitentan is a variably acting antagonist of both endothelin receptor types (A and B), so the drug affects not only the vascular tone, but also the stimulation of endothelial NO synthesis. Endothelin receptor antagonists are well-known for the successful treatment of pulmonary hypertension, with promising results also shown for essential hypertension [29].

Conclusion

Hypotensive treatment has undergone multiple changes and evolutionary steps, following the paths of understanding the disease pathogenesis, possibilities of effects with decreasing the risks of adverse events, increasing the life expectancy and quality of life. The majority of drug products was discarded due to new discoveries in pathophysiology and pharmacology. Currently studies are active on the management of EH and associated risks, expanding the clinical arsenal and getting closer to the era of the actual personalized medicine.

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