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THE EFFECT OF L-TYPE CALCIUM CHANNEL BLOCKERS ON AORTIC TONE

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R.M. Yunusova
M.Sh. Bakiyeva.
Namangan State University
Email: rayhonayunusova366@gmail.com

Annotation

The article presents modern concepts of the pathogenesis of arterial hypertension, its leading role in the development of cardiovascular diseases, and mechanisms associated with impaired calcium ion metabolism in vascular smooth muscle cells. Key factors in the development of hypertension, including increased tone of the aorta and large arteries, enhanced activity of L-type calcium channels, and alterations in endothelium-dependent vasoregulatory processes, are analyzed..

Key words

arterial hypertension, calcium ions, L-type calcium channels, aortic tone, calcium channel blockers, cardiovascular system.

ВЛИЯНИЕ БЛОКАТОРОВ L-ТИПА КАЛЬЦИЕВЫХ КАНАЛОВ НА ТОНУС АОРТЫ

Р.М. Юнусова, М.Ш. Бакиева.
Наманганский государственный университет
Email: rayhonayunusova366@gmail.com

Аннотация

В статье рассмотрены современные представления о патогенезе артериальной гипертензии, её ведущая роль в развитии сердечно-сосудистых заболеваний, а также механизмы, связанные с нарушением обмена ионов кальция в гладкомышечных клетках сосудистой стенки. В качестве основных факторов развития гипертензии проанализированы повышение тонуса аорты и крупных артерий, усиление активности кальциевых каналов L-типа и изменения эндотелий-зависимых процессов вазорегуляции.

Ключевые слова

артериальная гипертензия, ионы кальция, L-типа кальциевые каналы, тонус аорты, блокаторы кальциевых каналов, сердечно-сосудистая система.

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Introduction. According to statistics from the World Health Organization, currently over 1,000,000,000 people worldwide are affected by hypertension. Scientific and practical research continues to focus on understanding the pathogenesis of the disease and developing effective methods for its treatment and prevention. According to the American Heart Association, an average of 17,500 individuals die each year from cardiovascular diseases, and this number is projected to reach 23,500,000 by 2030. Thus, hypertension is considered one of the major factors in the pathogenesis of cardiovascular diseases globally. Hypertension is characterized by a marked increase in calcium levels in the vascular smooth muscle cells, which, in turn, affects the activity of L-type calcium channels and modulates endothelium-dependent reaction cascades. These mechanisms play a critical role in antihypertensive therapy.

The aorta is the largest arterial vessel emerging from the heart and plays a critical role in shaping and maintaining arterial blood pressure. One of its primary functions is to receive the blood ejected during ventricular contraction and, through elastic recoil during diastole, to ensure continuous blood flow. Therefore, the functional state of the aorta directly influences arterial pressure. Aortic elasticity is one of the key factors regulating arterial blood pressure.

Moreover, hemodynamic changes in the aorta indirectly affect renal circulation. Variations in blood flow through the aorta to the renal arteries can lead to activation of the renin–angiotensin–aldosterone system (RAAS). RAAS activation results in vasoconstriction and retention of sodium and water, which further contributes to elevated arterial pressure.

The wall of the aorta contains smooth muscle cells, which determine the aortic tone, i.e., the degree of constriction or dilation of the vessel. When aortic tone is high, the artery constricts, leading to an increase in blood pressure; conversely, when the smooth muscles relax, the aorta dilates, and blood pressure decreases. Therefore, contraction and relaxation of aortic smooth muscle are critical for the proper functioning of the cardiovascular system.

Contraction of aortic smooth muscle is dependent on calcium ions (Ca^{2+}). Under normal conditions, calcium channels in the cell membrane open, allowing Ca^{2+} to enter the cell. The incoming calcium ions bind to the myofibrillar system, inducing contraction of the muscle fibers. Within the myofibrillar system, troponin and actin–myosin proteins become activated, resulting in strong muscle contraction. Consequently, the aortic wall narrows, blood pressure rises, and the cardiac muscles must work with greater force.

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Calcium ions (Ca^{2+}) are considered the primary regulators of the cardiovascular system. They control heart rhythm, facilitate the contraction of myocardial cells, and regulate vascular wall tone. Therefore, the proper functioning of calcium channels is essential for the activity of the heart and aorta.

Calcium channels are voltage-gated ion channels located in the cell membrane, and their main function is to regulate various physiological processes by allowing the influx of Ca^{2+} ions into the cell. In the heart and blood vessels, calcium channels control arterial tone, heart rate, and contractile activity.

In 1953, Paul Fatt and Bernard Katz discovered voltage-dependent calcium channels in crustacean muscle. These channels differ in their activation voltages and calcium-conducting properties, and were therefore classified into high voltage-activated (HVA) and low voltage-activated (LVA) channels. Subsequent experiments demonstrated that HVA channels can be blocked by 1,4-dihydropyridine (DHP) derivatives. Studies using DHP further revealed that HVA channels are tissue-specific and exhibit variable responses. In cardiac and vascular cells, three main types of calcium channels are present:

1. **L-type calcium channels (Long-lasting type)** are high-voltage-activated channels that remain active for a prolonged period. They play a crucial role in the cardiovascular system. These channels open at high membrane potentials, allowing Ca^{2+} ions to enter the cell for an extended duration. L-type channels are widely distributed in cardiac muscle, smooth muscle, and arteries. They enhance myocardial contraction, increase arterial tone, regulate blood pressure, and facilitate signal transmission in neurons.

Types of L-type calcium channels located in the smooth muscle cells of the aortic wall:

1.$Ca_v1.2$ (a1C) – the primary and predominant type

This is the most abundant and functionally significant L-type Ca^{2+} channel in aortic smooth muscle cells. Its characteristics include: activation at high voltages, facilitation of prolonged Ca^{2+} influx into the cell, promotion of actin–myosin interaction and muscle contraction, and induction of vasoconstriction and increased peripheral vascular resistance. Consequently, in arterial hypertension, the expression and activity of $Ca_v1.2$ channels are elevated.

Calcium channel blockers of the dihydropyridine group (e.g., nifedipine, amlodipine) specifically block this channel.

2.$Ca_v1.3$ (a1D) — the less abundantly expressed type

$Ca_v1.3$ channels are present in small amounts in aortic smooth muscle cells but are functionally significant. Their characteristics include: activation at relatively lower membrane potentials, participation in maintaining basal vascular tone, and

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provision of a slow and steady Ca^{2+} influx. Consequently, these channels help support vascular tone at rest and may increase sensitivity to sympathetic stimulation.

3. Auxiliary subunits of L-type Ca^{2+} channels (β, a_2δ, γ)

In aortic smooth muscle cells, L-type Ca^{2+} channels are not composed solely of the α1 subunit but form a complex with several auxiliary subunits:

- **β subunit** — facilitates trafficking of the channel to the membrane and regulates its kinetics
- **$\alpha_2\delta$ subunit** — increases the probability of channel opening
- **γ subunit** — acts as a modulator (less well studied)

The expression of these subunits may change in hypertension and vascular remodeling. In aortic smooth muscle cells, the main functional types of L-type Ca^{2+} channels are **$Ca_v1.2$** and, to a lesser extent, **$Ca_v1.3$**. Their activity determines vascular tone, vasoconstriction, and arterial blood pressure. Notably, $Ca_v1.2$ channels play a central role in the pathogenesis of arterial hypertension and represent an important target for modern antihypertensive therapy.

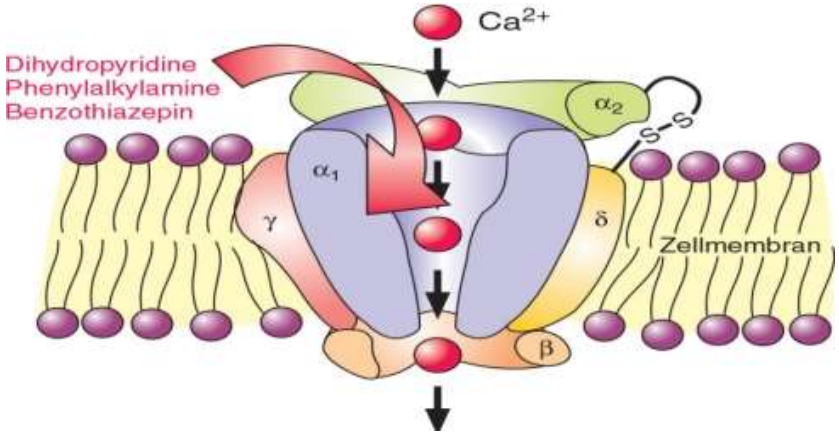

Figure 1. Schematic representation of a Ca^{2+} channel.

2 **T-type calcium channels (Transient type)** are low-voltage-activated channels that open and close rapidly. The letter "T" stands for "Transient." These channels are activated at low membrane potentials, close quickly, and function only for a short duration. They are present in cardiac nodal cells, the brain, and β-cells. Functionally, T-type channels are involved in controlling and regulating heart rhythm, transmitting rhythmic signals in neurons, and generating small basal tone in the smooth muscle of the aorta and arteries.

3. **N-type calcium channels (Neuronal type)** are high-voltage-activated channels primarily functioning in the nervous system. The letter "N" stands for "Neuronal." These channels are found in both the central and peripheral nervous systems, where they regulate synaptic transmission and control the release of neurotransmitters. Their functions include transmitting pain signals, enhancing

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signal propagation in neurons, and influencing the activity of certain endocrine systems.

Figure 2. Sites of action of calcium channel blockers in arterial smooth muscle.

Calcium channel blockers (CCBs) are a heterogeneous group of drugs that share a common mechanism of action but differ in pharmacokinetics, tissue selectivity, effects on heart rate (HR), and other properties. They prevent excessive contraction of smooth muscle. These drugs block or slow the activity of L-type and T-type calcium channels, resulting in reduced Ca^{2+} influx into the cell. The decreased calcium entry slows the activity of the myofibrillar system, reducing the activity of troponin and actin–myosin proteins, which leads to muscle relaxation. Consequently, CCBs lower blood pressure, relax vascular walls, and improve blood circulation.

Additionally, CCBs have cardioprotective and vasoprotective effects, reducing the risk of myocardial infarction, stroke, and other complications. In the United States, CCBs, particularly amlodipine, are among the most commonly used drugs for the treatment of cardiovascular diseases.

The first clinically significant calcium antagonist was **verapamil**, which was developed in 1961 as a result of attempts to synthesize active analogs of papaverine with vasodilatory effects. **Nifedipine** was synthesized in 1966, followed by **diltiazem** in 1971. Verapamil, nifedipine, and diltiazem are the most extensively studied representatives of calcium antagonists and are considered prototype drugs. The characteristics of new drugs in this class are generally compared to these prototypes.

In 1962, Hass and Hartfelder discovered that **verapamil** not only dilates blood vessels but also exerts negative inotropic and chronotropic effects, unlike other vasodilators such as nitroglycerin. By the late 1960s, A. Fleckenstein proposed that the effects of verapamil on cardiomyocytes were associated with a reduction in Ca^{2+} influx. Studies in animals showed that the action of verapamil was equivalent to

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removing Ca^{2+} ions from the perfusion medium; when Ca^{2+} was added, the cardiodepressive effects of verapamil disappeared. During this period, related compounds such as **prenylamine** and **gallopamil** were proposed to be classified as calcium antagonists.

Subsequent studies revealed that certain drugs from various pharmacological groups also possess the ability to moderately influence the entry of Ca^{2+} ions into cells (e.g., **phenytoin**, **propranolol**, **indomethacin**).

L-type calcium channels (long-lasting, large-capacitance) are slowly activated during depolarization of the cell membrane, allowing gradual Ca^{2+} influx and contributing, for example, to the formation of the slow calcium potential in cardiomyocytes. L-type channels are located in cardiomyocytes, cells of the cardiac conduction system, smooth muscle cells of arteries and bronchi, as well as in the uterus, urinary tract, gallbladder, gastrointestinal tract, skeletal muscle cells, and platelets.

There are numerous classifications of calcium channel blockers (CCBs) based on chemical structure, tissue selectivity, duration of action, and other properties. The most widely used classification reflects the chemical heterogeneity of calcium antagonists.

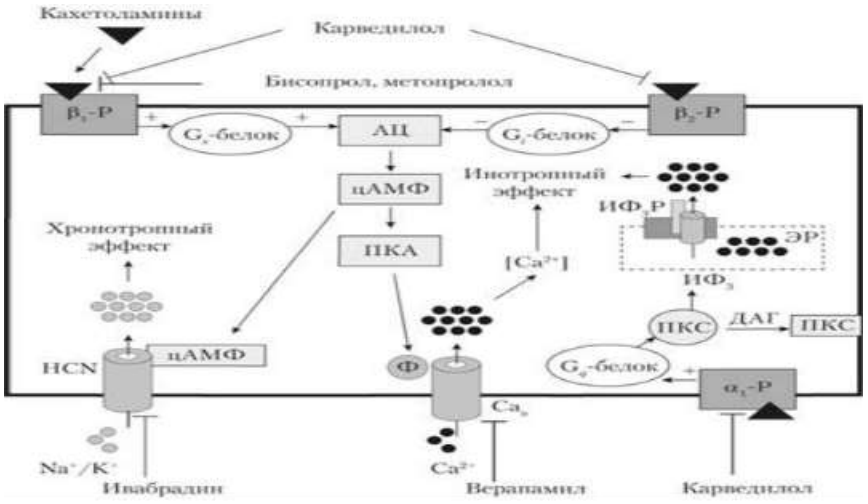

Figure 3. Molecular mechanisms of action of inhibitors (ivabradine) and β-adrenoceptor blockers (bisoprolol, metoprolol, carvedilol).

Based on chemical structure, L-type calcium antagonists are generally classified into the following groups:

1. **Phenylalkylamines** (e.g., verapamil, gallopamil, etc.)
2. **1,4-Dihydropyridines** (e.g., nifedipine, nitrendipine, nimodipine, amlodipine, lacidipine, felodipine, nicardipine, isradipine, etc.)
3. **Benzothiazepines** (e.g., diltiazem, clentiazem, etc.)
4. **Diphenylpiperazines** (e.g., cinnarizine, flunarizine)
5. **Diarylaminopropylamines** (e.g., bepridil)

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From a practical perspective, based on their effects on sympathetic nervous system tone and heart rate, calcium antagonists can be divided into two subgroups: those that reflexively increase heart rate (derivatives of dihydropyridines) and those that decrease heart rate (e.g., verapamil and diltiazem, whose effects are in many ways similar to those of β-adrenoceptor blockers).

Unlike dihydropyridines, **phenylalkylamines** and **benzothiazepines** exert negative inotropic effects (reducing myocardial contractility) and negative chronotropic effects (slowing heart rate).

According to the classification proposed by I.B. Mikhailov (2001), calcium channel blockers (CCBs) are divided into three generations:

First generation:

a) **Verapamil** (Isoptin, Finoptin) — a derivative of **phenylalkylamines**
b) **Nifedipine** (Fenigidin, Adalat, Corinfar, Cordafen, Cordipine) — a derivative of **dihydropyridines**

c) **Diltiazem** (Diazem, Diltiazem) — a derivative of **benzothiazepines**

Second generation:

a) **Verapamil group:** gallopamil, anipamil, falipamil
b) **Nifedipine group:** isradipine (Lomir), amlodipine (Norvasc), felodipine (Plendil), nitrendipine (Octidipin), nimodipine (Nimotop), nicardipine, lacidipine (Lacipil), riodipine (Foridon)

c) **Diltiazem group:** clentiazem

The primary mechanism of action of **calcium channel blockers (calcium antagonists)** is the inhibition of Ca^{2+} ion entry into cardiac and vascular smooth muscle cells via L-type calcium channels. By reducing Ca^{2+} concentration in cardiomyocytes and vascular smooth muscle cells, these drugs promote dilation of the coronary and peripheral arteries as well as arterioles, producing pronounced vasodilation.

The pharmacological activity spectrum of calcium antagonists includes modulation of myocardial contractility, sinus node activity, vascular tone and resistance, as well as the function of the bronchi, gastrointestinal tract, and urinary system. Additionally, these agents can slow platelet aggregation and modulate neurotransmitter release from presynaptic nerve terminals.

In conclusion, calcium channel blockers that modulate the activity of L-type calcium channels represent effective and reliable therapeutic agents targeting key mechanisms in the pathogenesis of arterial hypertension. Their appropriate selection based on an individualized clinical approach, combined with regular monitoring, is crucial for reducing the risk of cardiovascular complications and improving patients' quality of life.

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