ევა: ანამნეზის დეტალური ანალიზი, ზოგადი კლინიკური კვლევა, ნევროლოგიური სტატუსის კვლევა, ლაბორატორიული და ინსტრუმენტული კვლევები.

თირკმლის, ღვიძლის და იმუნოლოგიური პარამეტრების ანალიზის შედეგად გვერდითი ამიოტროფული სკლეროზის და დიუშენის მიოდისტროფიის მქონე პაციენტებში გამოვლინდა თირკმლების დაზიანების ნიშნები.

გვერდითი ამიოტროფული სკლეროზით პაციენტების 69%-ში შრატის კრეატინინის დონე ნორმაზე დაბალი იყო, ხოლო პაციენტების 5,5%-ში – ნორმაზე მაღალი. მსგავსი სიტუაცია აღინიშნა პაციენტებში დიუშენის მიოდისტროფიით: 58,5%-ში შრატის კრეატინინის დონე ნორმაზე დაბალი იყო, ხოლო პაციენტების 3,8%-ში – ნორმაზე მაღალი.

შარდოვანას დონე სისხლის შრატში ამიოტრო-ფული სკლეროზით პაციენტების უმეტესობას (89,1%) და დიუშენის მიოდისტროფიით ყველა პაციენტს ჰქონდა რეფერენტული მაჩვენებლების ფარგლებში.

გვერდითი ამიოტროფული სკლეროზით პაციენტების უმეტესობას და დიუშენის მიოდისტროფიით ყველა პაციენტს პირველადი მიმართვისას და განმეორებითი გამოკვლევისას ერთი წლის შემდეგ გორგლოვანი ფილტრაციის სიჩქარე ჰქონდა რეფერენტული მაჩვენებლების ფარგლებში, თუმცა, გვერდითი ამიოტროფული სკლეროზის მქონე პაციენტების 21,8%-ს აღენიშნა თირკმლების ფილტრაციულ-მაკონცენტრირებელი ფუნქციის მსუბუქი დარღვევა, 5,5%-ს კი – ზომიერი დარღვევა. გამოვლინდა სუსტი დადებითი კავშირი გორგლოვან ფილტრაციას და სიცოცხლის ხანგრძლივობას შორის გვერდითი ამიოტროფული სკლეროზით პაციენტებში ($r=0.28$, $p<0.01$). კავშირი შრატის კრეატინინის დონესა და პარეზის ხარისხს შორის გვერდითი ამიოტროფული სკლეროზით პაციენტებში არ გამოვლინდა, რაც ეწინააღმდეგება ინეს მარტინის მიერ 2020 წელს მიღებულ მონაცემებს.

იმუნური სტატუსის მნიშვნელოვანი ცვლილებები დადგინდა გვერდითი ამიოტროფული სკლეროზით პაციენტებში: თითქმის ყველა პაციენტს (94,5%) დაუდგინდა B-ლიმფოციტების დონის შემცირება, პაციენტების 41,8%-ს დაუფიქსირდა T-ლიმფოციტების ერთ-ერთი სუბპოპულაციის - T-სუპრესორების – დონის დაქვეითება.

გვერდითი ამიოტროფული სკლეროზის და დიუშენის მიოდისტროფიის მქონე პაციენტებში ჩატარებული კომპლექსური ლონგიტუდინური კვლევით გამოვლინდა ამ პაციენტებში პროგნოზული თვალსაზრისით მნიშვნელოვანი ცვლილებები თირკმლის ფუნქციის პარამეტრების მხრივ. გვერდითი ამიოტროფული სკლეროზით პაციენტებში გამოვლინდა იმუნური სტატუსის T- და B-უჯრედული კომპონენტების და ფერმენტული სისტემების პარამეტრების გადახრა, სახელდობრ, ლაქტატდეჰიდროგენაზას და ასპარტატდეჰიდროგენაზას მაჩვენებლების, რომელთა ხასიათი და პროგნოზული მნიშვნელობის დადგენა შემდგომ კვლევას საჭიროებს.

THE MECHANISMS CONTRIBUTING TO THE DEVELOPMENT OF ARTERIAL HYPERTENSION, ADVANTAGES AND DISADVANTAGES OF THE ASSOCIATED EXPERIMENTAL MODELS (REVIEW)

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Arterial hypertension is the most important modifiable risk factor for cardiovascular diseases. Its asymptomatic course causes adverse health outcomes such as stroke, ischemic heart disease, and heart failure. Several classes of basic medications are currently used against hypertension, including, but not limited to, angiotensin-converting enzyme (ACE) inhibitors, angiotensin 1 receptor (AT1) antagonists, beta-blockers, calcium channel blockers, and diuretics. However, sometimes, these drugs do not adequately control blood pressure. Additionally, their use may be limited due to patient comorbidities. It is currently estimated that 10-15% of patients with hypertension are resistant to existing antihypertensive drugs[1]. Therefore, the development of a new approach to the treatment of hypertension is essential to prevent end-organ damage. Remodeling of the cardiovascular system plays a key role in the clinical course of hypertension. Several factors contribute to cardiovascular remodelings such as increased production of vasoconstrictor agents and inflammatory cytokines, endothelial dysfunction, myocardial hypertrophy, and oxidative stress [2,3].

The importance of the renin-angiotensin system in the pathophysiology of circadian blood pressure has been established. Though inflammation is increasingly associated with damage to blood vessels and elevation in blood pressure, it is still unclear what mechanism activates the immune processes and leads to the development of inflammation during hypertension. High blood pressure can lead to a molecular picture characteristic of the lesion, which is detected by the corresponding receptors and activates the innate immune system, and on the other hand, promotes the activation of the adaptive immune system by neoantigens. The imbalance between T-effector and T-regulator lymphocytes is followed by an inflammatory response and vascular remodeling [4]. Certain genetic predisposition and unfavorable environmental conditions (e.g. excess salt) activate the sympathetic nervous system, leading to hypertension. According to the available data, oxidative stress and the expression of genes involved in the inflammatory process are actively involved in the remodeling of blood vessels and the damage to related organs. Based on modern studies, inflammation and activation of the immune system play a leading role in damaging target organs caused by hypertension, especially blood vessels and myocardium [2].

Vascular remodeling is an active process that involves four cellular processes: cell growth, cell death, cell migration, and extracellular matrix synthesis and degradation. It is related to the dynamic interaction of local growth factors, vasoactive substances, and hemodynamic stimuli and develops in response to prolonged changes in hemodynamic parameters. However, it is not only the hemodynamic process that causes vascular remodeling. The inflammatory response and the change in the components of the matrix are also important mediators in the process of vascular adaptation [3].

In response to hypertensive stimuli, such as activation of the renin-angiotensin-aldosterone system, excess salt, oxidative stress, and inflammation, there is a sharp rise in blood pressure, leading to protein modification. As a result, T cells are activated, and through appropriate signaling mechanisms, macrophages and other inflammatory cells move to the blood vessels and kidneys and release cytokines. In particular, increased levels of TNF-a, IL-1, and IL-6 were detected [5]. T cell activation is followed by narrowing and remodeling of blood vessels.

One of the mechanisms of inflammation and endothelial dysfunction in hypertension may be related to nitric oxide, which is involved in regulating the tone and structure of blood vessels.

Prolonged inflammation leads to the development of oxidative stress, which is a major cause of endothelial dysfunction and can affect the activity of vasodilators and vasoconstrictors, particularly nitric oxide synthase (eNOS) and nitric oxide products. Both C-reactive protein and TNF-α acts on eNOS and reduces its production. IL-17 induces endothelial dysfunction by activating Rho-kinase, which also has an inhibitory effect on eNOS. Oxidative stress induces the development of the inflammatory process as well as activation of the NF-kB transcription factor [6].

It has been shown, that an increase in the amount of pro-inflammatory cytokines and a change in the composition of the extracellular matrix contribute to the differentiation of cardiac fibroblasts into activated myofibroblasts. It contributes to myocardial fibrosis and has other damaging consequences. In particular, inflammation is crucial for the development of fibrous changes and diastolic dysfunction in a hypertensive heart [7-9].

Based on the above, the study of the effect of investigational agents as a modulators of RAAS system of endothelial dysfunction, hemodynamic instability, and the development of cardiovascular remodeling requires to create the corresponding models of arterial hypertension.

Small animal models are the most commonly used models that provide deep insights. For example, these models can target particular factors such as salt sensitivity and activation of the renin-angiotensin-aldosterone system (RAAS). Rats and mice offer several advantages over larger animal models, including a short gestation period and cost-effectiveness. However, there are several setbacks: reliable blood pressure measurement, as well as surgical procedures, are difficult in small animals and the amount of available urine and plasma samples available can be limiting. However, development in imaging and surgical procedures has solved some of these issues.

Rodent models give ready availability of techniques for precise genetic changes through whole-body or cell-specific gene deletions (knockout) or gene editing. These techniques allow studies to elaborate on molecular mechanisms and to find new therapeutical targets for therapy. Another advantage of the rat is the existence of many genetic strains that exhibit strong spontaneous hypertensive phenotypes at baseline or through induction by environmental conditions. Moreover, the rat is easy and cost-effective to maintain and breed yet large enough for long-term studies, and blood and tissue sampling. Rat models express many phenotypic traits seen in human hypertension. For this reason, they are used to examine both the genetic and mechanistic bases of hypertension. In recent years, many techniques of physiological monitoring have been adapted to mice, which have lower experimental and maintenance expenses compared with rats. In addition, a very wide range of specific antibodies is available commercially for mice (Fig.).

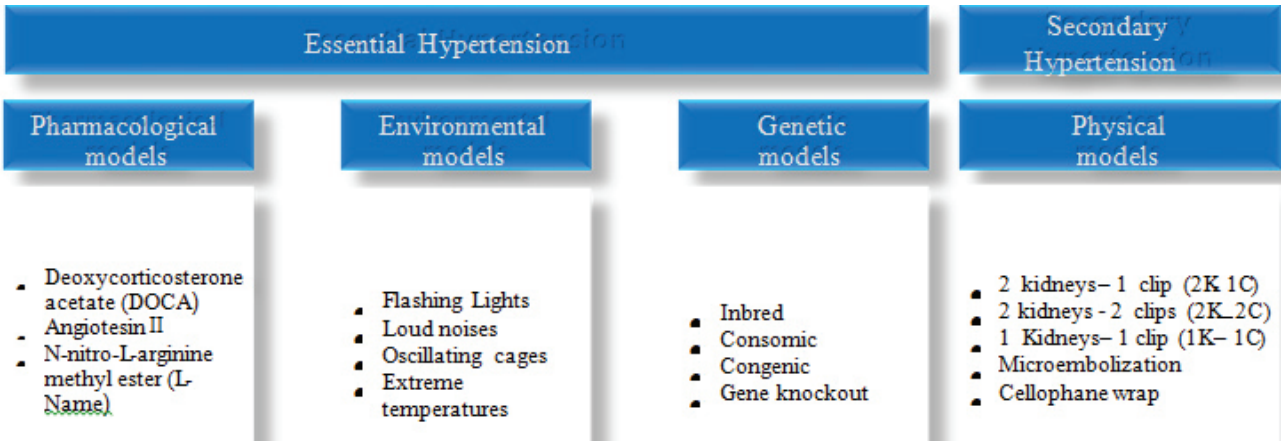

Fig. Different experimental models of essential and secondary hypertension

Major advantages of large animal models such as primate or pig are their anatomic and hemodynamic similarities to humans, combined with developmental pathophysiology in hypertension that might more closely resemble humans compared with small animal models. Large animals are also suitable for linear studies of hemodynamic outcomes of long-term hypertension. They also have an added advantage for repeated sampling of plasma and abundant tissues in which to quantify and often follow functional and structural injury in target organs. Therefore, longitudinal data may be collected from the same animal. A major disadvantage is the limited availability of large animal models of hypertension compared with that of rodents. This is mostly due to higher costs of maintenance and labor-intensive experiments on large animals. Finally, ethical issues have been a great concern for studies using nonhuman primates.

The most frequently used large animals to study hypertension are nonhuman primates, sheep, pigs, and dogs. Induction of hypertension typically necessitates pharmacological or surgical approaches. Pharmacological interventions using long-term infusions of glucocorticoids, angiotensin II, or DOCA (with and without high-salt diet) in pigs or dogs are less commonly used than in smaller animals, partly due to high cost of body size–titrated doses of drugs required over prolonged periods. On the other hand, surgical induction of hypertension is relatively simple and well-tolerated. These interventions include constricting aorta with extravascular banding, implantable adjustable occluders in the suprarenal aorta or renal arteries, or intravascular devices in the renal arteries. These methods create appropriate models of chronic hypertension mainly of renovascular origin. The use of adjustable occluders to restrict blood flow allows the degree of insult to be controlled, which can be used to determine the extent of BP elevation required to trigger target-organ injury. Intra-arterial devices such as coils that progressively narrow the renal arterial lumen may mirror the obstructive plaques in human renal artery stenosis and thus more closely recreate the pathophysiology of this disease. The degree of obstruction and target-organ injury created by intravascular devices is often variable. Finally, recent data show that African green monkeys can be used as a model of spontaneous hypertension. Hypertension in this model develops without external interventions and is associated with target-organ injury [10].

There are several reasons why animals are widely used in biomedical research, among which is feasibility. They are relatively easy to manage, as many modifiable effects such as dietary intake, environmental factors (temperature, lighting) can be easily controlled. That's why environmental variation compared to human studies is minimal. Also, it is very simple to isolate blood vessels and cardiac tissues can for detailed experimental and biomolecular investigations when needed. Another benefit is their shorter life span compared to humans. Therefore, they can be studied over their whole life cycle or even across several generations, making animals the best study models. In addition, many animals have similarities in anatomical basis and physiological functions with humans. For example, chimpanzees and mice share about 99% and 98% of DNA with humans, respectively. Therefore, animals share many health problems afflicting humans. As a result, animals are good models for the study of human diseases [11].

Before initiating the study on animals, researchers must be sure that animals are essential for their experiments, with no viable alternatives. Russell and Burch first introduced the use of the 3Rs principle relating to animal research in 1959 and has been a practice since then. The 3Rs refer to a replacement, reduction, and refinement. Replacement refers to conducting experiments using non-animal models whenever possible, for instance, in vitro method with cell culture or with computer model simulation (in silico). However, the information obtained from in vitro is typically much limited compared to in vivo studies. Reduction means the need for reducing the number of animals, either from previous studies or by using the calculation of size sample with a good experimental design. Refinement stands for the efforts to minimize pain and suffering of test animals, taking into consideration animal handling and surgical procedures, housing environment and living conditions, and improvements in animal husbandry. The aim of the 3Rs is to provide humane and scientifically refined research involving or avoiding the use of animal models. There are available guidelines for reporting animal studies to justify the of using animals, such as the Animals in Research: Reporting In Vivo Experiments (ARRIVE) guidelines and the Gold Standard Publication Checklist (GSPC) [11].

Excellent animal models have been established for many of the rare causes of hypertension [10;11]. However, as the etiology of primary hypertension is unclear, models of this condition have been more burdensome to develop. Nearly 50% of National Institutes of Health-sponsored hypertension research are based on studies using Ang II (angiotensin II) infusion,[12] while only 4% of studies focus on aging and 4% focus on DOCA (deoxycorticosterone acetate)–salt hypertension (which itself does not mimic primary hyperaldosteronism). Hence, it is crucial to promote better animal models which will more closely mimic the discrete hypertensive syndromes that are regularly encountered in clinics such as primary hyperaldosteronism [13].

There are several criteria that should be taken into consideration to develop an ideal animal model for hypertension. These factors include the feasibility, size of the animals, their reproducibility, the ability to predict the potential antihypertensive properties of a drug, the similarity to human disease (acute or chronic), economical, technical, and animal welfare considerations [14,15]. Though in the past, dogs were mostly employed as a model to study hypertension, the preferred animal model in the rat, currently. Along with rats, occasionally mice, monkeys, and pigs are also used [16,17], which have not been studied extensively for both practical and financial reasons. In 1963, Okamoto and Aoki introduced an experimental hypertension model, known as the spontaneously hypertensive rat (SHR), without the involvement of physiological, pharmacological, or surgical intervention. SHR has become the animal of choice for the screening of antihypertensive agents and the cornerstone and the main focus of medical research in experimental hypertension. The benefits of this models are the short life span, small size, and relatively low cost, which let the researchers study the natural history, genetic factors, and pathophysiological changes in hypertension. There are other strains that have been developed, including the New Zealand strain [18,19], Milan strain, Dahl salt-sensitive strain [20], Sabra strain, and Lyon strain [21,22].

The most frequently encountered human type of hypertension is Essential hypertension, also known as primary hypertension. It contributes to 95% of incidences and is associated with genetic influences. Even though SHR represents only a particular type of hypertension, it is frequently used among the many strains of rat models [23].

Renovascular hypertension is a commonly employed model of hypertension, for which RAAS is a cornerstone [24,25]. In 1934, Goldblatt et al. developed a hypertension model through partial constriction of the renal artery in dogs. This has led to other renal-induced hypertension models using rats, rabbits, sheep, and cats. Renal artery ligation or constriction manifests

in RAAS and the sympathetic nervous system activation. Renin is secreted by the kidneys in response to sympathetic nervous system activation. It is responsible for the conversion of angiotensinogen to angiotensin I (Ang I). Angiotensin-converting enzyme (ACE), mostly located on the surface of the endothelium and epithelium, has great importance in blood pressure regulation through hydrolysis of the inactive form of angiotensin I to the active form, angiotensin II (Ang II). Ang II is not only a potent vasoconstrictor but also stimulates the secretion of aldosterone, which itself further increases blood volume and BP via salt and water retention. On contrary, nitric oxide (NO) is a potent vasodilator, released from the endothelium in response to vasoactive substances like acetylcholine (ACh). Therefore, NO just like Ang II plays an important role in cardiovascular homeostasis and blood pressure regulation.

Nitric oxide synthase (NOS) catalyzes the synthesis of NO. The deficiency of NOS and thus, reduced NO bioavailability will cause decreased endothelium-dependent vasorelaxation, eventually leading to hypertension. Infusion of L-arginine, which activates eNOS, does not completely reverse L-NAME–induced hypertension. It means that the mechanisms underlying L-NAME–induced hypertension involve processes beyond inhibition of endothelium-derived NO and direct effects on the vascular tone. In particular, persistent inhibition of NO biosynthesis with L-NAME causes profound vasoconstriction, activation of the sympathetic nervous system and RAAS, cardiac and aortic damage, renal hypertensive microangiopathy, and glomerular fibrosis. Since RAAS inhibitors do not completely ameliorate L-NAME–induced hypertension, other humoral factors such as ET-1 have also been discussed [30].

The study, conducted by Soriguer et al. on cooking oils, showed that repeatedly oxidized frying oil is an independent risk factor for hypertension. It means that the degradation of dietary frying oil is related to hypertension. Previously, adult male Sprague-Dawley rats aged 3 months were administered with 15% weight/weight (w/w) of repeatedly heated vegetable oils for 16 weeks or 24 weeks [26-29], resulting in increased BP. The BP-raising effect of the heated vegetable oils can be contributed by the diminished endothelium-dependent relaxation responses. A heated oil diet increases oxidative stress, leading to NO sequestration and inactivation. Moreover, heated oil increases ACE activity and reduces heme oxygenase content. The thermal oxidation of vegetable oils generates free radicals and may be attributable to the pathogenesis of hypertension in rats. This heated oil-induced hypertension model was observed in male instead of female rats, as female hormones have cardioprotective properties [12,13].

As discussed previously, the RAAS is the major regulator of cardiovascular homeostasis. Thus, one of the long-established preclinical models of hypertension, especially in rodents, is a long-term subcutaneous infusion of angiotensin II. The utility of this model is in the resemblance of some forms of human hypertension. End-organ damage after 4 weeks of long-term Ang II infusion in susceptible rodent strains is similar to that seen in patients with sustained HTN, including cardiac hypertrophy, vascular remodeling, and chronic kidney disease [31-34]. Moreover, long-term Ang II infusion more closely mimics the renal injury caused by HTN-induced chronic renal ischemia than that by barotraumas [35]. It is easily explained by ATII-induced renal vasoconstrictive properties which can induce ischemia.

Hypertension can be provoked by the administration of mineralocorticoids along with high-salt diet in large as well as small animals. In animals with a high salt intake, administration of deoxycorticosterone, particularly in the form of DOCA, is the most widely used approach for inducing mineralocorticoid-salt hypertension. Deoxycorticosterone has glucocorticoid as well as mineralocorticoid abilities, but its property to cause sodium retention is key to the DOCA-salt model. It has less mineralocorticoid potency aldosterone, though. Owing to the fact that the most common human form of mineralocorticoid-dependent hypertension is hyperaldosteronism, the establishment of animal models of hyperaldosteronism is a subject of scientific motif. By transgenically expressing the human gene for aldosterone synthase under control of the human promoter for the gene encoding 11β hydroxylase, a mouse model of aldosterone-salt hypertension was developed recently.

Aiming to investigate the adaptive effects of renal mass reduction on the remaining nephrons, remnant kidney models were originated in rats. It clearly revealed the destructive effects of glomerular hyperfiltration and the benefits of lowering glomerular pressure via RAAS inhibition, providing a rationale for the use of RAAS blockers in hypertensive patients with chronic kidney diseases. Extrapolation from these rat models showed, that infarction of two-thirds of 1 rat kidney results in BP elevation, while two-thirds nephrectomy in addition to total contralateral nephrectomy (the modern subtotal nephrectomy model) causes both hypertension and glomerulosclerosis.

Two-thirds of nephrectomy in rats is generally conducted on the left kidney. It is accomplished by ligation of the posterior branch and the inferior segment of the renal artery. In mice, the procedure is technically challenging, as it typically requires a three-fourths nephrectomy (1 nephrectomy plus resection of half the contralateral kidney). Nevertheless, it has been performed with ligation of renal artery segments as in rats or with direct excision of half a kidney with electrocautery or glue used in order to achieve hemostasis.

Though hypertension invariably develops in remnant kidney rats, subtotal nephrectomy in mice causes hypertension in the 129SVE salt-sensitive strain but not in the relatively salt-resistant C57BL/6 strain [36]. In this model, in long-term studies, hypertension and kidney disease progress more slowly and less severely than in the more aggressive pharmacological hypertension model. While tail-cuff plethysmography may be enough to monitor a rise in BP in rats, radiotelemetry is recommended for BP assessment in mice, because of the response variability in these rodents. Reliable measurement of blood pressure in conscious mice is essential in cardiovascular research. Telemetry, the “gold-standard” technique, is invasive and expensive and therefore tail-cuff, a noninvasive alternative, is widely used [37].

The conventional tail-cuff method was used for BP measurement, even though invasive methods such as carotid arterial cannulation may provide more accurate readings. However, those invasive techniques can cause injury in the animals and further complicate the study. In addition, these studies aimed to compare and monitor the effects of heated oil diets among the experimental groups up to 24 weeks using a large number of rats. Therefore, the noninvasive tail-cuff method is more suitable for measuring blood pressure for long-term studies.

Conclusion. In conclusion, various pharmacological, physical and genetic models using different animal species have provided useful and valuable information about the etiology, pathophysiology and metabolic complications of human cardiovascular diseases. However, the main limitation of these experimental models is the anatomic difference between these animals and humans. Although the main mechanism is to active the rennin-angiotensin-aldosterone system in different species, they must be carefully se-

lected to ensure the safety of new pharmacological agents. Considering the advantages and disadvantages discussed in the article, the experimental animals and the triggering mechanisms of the hypertensive model should be selected thoroughly.

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SUMMARY

THE MECHANISMS CONTRIBUTING TO THE DEVELOPMENT OF ARTERIAL HYPERTENSION, ADVANTAGES AND DISADVANTAGES OF THE ASSOCIATED EXPERIMENTAL MODELS (REVIEW)

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Arterial hypertension is one of most common diseases in the world with variable etiologies, yet the exact cause cannot always be found. It is classified as essential (primary) or secondary hypertension. Unlike secondary hypertension, primary hypertension has no known cause. Animal models have been used to investigate the pathophysiology of the disease and for testing new treatment strategies. Using animal models to better understand the etiology, prevention, and treatment of hypertension depends on their accuracy for representing human disease. Current challenges in this field include the development of models mimicking the common hypertensive syndromes and the development of new prevention and treatment strategies. Animal models may be beneficial to address these challenges.

While choosing the appropriate model of hypertension, scientists need to choose between small and large animal models. The research scope and objectives, experimental expenses, animal welfare, and practical suitability should all be considered. The advantages and disadvantages of these models need to be assessed in detail in order to select the best model. From the many models of arterial hypertension, it can be distinguish different models of essential and secondary arterial hypertension. Of the essential arterial hypertension three main methods are noteworthy, pharmacological, environmental conditions, and genetic model. As for secondary hypertension, it can be challenged by physical methods such as renal artery clipping or its microembolization.

Keywords: arterial hypertension, experimental models, renin-angiotensin-aldosterone system.

РЕЗЮМЕ

МЕХАНИЗМЫ, СПОСОБСТВУЮЩИЕ РАЗВИТИЮ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ, ПРЕИМУЩЕСТВА И НЕДОСТАТКИ РАЗЛИЧНЫХ МОДЕЛЕЙ ЭКСПЕРИМЕНТАЛЬНОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ (ОБЗОР)

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Артериальная гипертензия - одно из наиболее распространённых заболеваний в мире. Различают эссенциальную, т.е. первичную и вторичную гипертензию. В отличие от вторичной, этиология первичной гипертензии по сей день не изучена. Модели на животных используются для исследования патофизиологии гипертензии и новых стратегий лечения. Поэтому, важно сначало же подобрать подходящую модель, которая наилучшим образом отражает течение болезни в организме человека и позволит сделать правильные заключения по поводу разработки новых методов профилактики и стратегий лечения.

В первую очередь, необходимо определить на каких животных, больших или маленьких, будут проводится эксперименты. Это зависит от цели и задач исследования, возможных расходов, этических норм экспериментов на животных и практических условий, т.е. изначально следует оценить положительные и отрицательные стороны уже известных моделей.

В статье детально охарактеризованы экспериментальные модели артериальной гипертензии, которые разделены на две большие группы: первичная и вторичная. При моделировании первичной гипертензии используются три подхода: фармакологический, с помощью воздействия внешних факторов и генетический метод. Вторичную гипертензию моделируют оперативным методом клипирования почечной артерии или её микроэмболизацией.

რეზიუმე

არტერიული ჰიპერტენზიის განვითარების მექანიზმები და სხვადასხვა ექსპერიმენტული მოდელის დადებითი და უარყოფითი მხარეები (მიმოხილვა)

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თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, სამედიცინო ფარმაკოლოგიის დეპარტამენტი; *კვლევის მონაწილეები, დიპლომირებული მედიკოსის ამერიკული პროგრამა, საქართველო

არტერიული ჰიპერტენზია ერთ-ერთი ყველაზე გავრცელებული დაავადებაა მსოფლიოში. განას-

ხვავებენ ესენციურ ანუ პირველად და სიმპტომურ ჰიპერტენზიას. მეორადისგან განსხვავებით ესენციური ჰიპერტენზიის ზუსტი ეტიოლოგია არ არის დადგენილი. დაავადების ცხოველური მოდელი გამოიყენება პათოფიზიოლოგიური მექანიზმების და მკურნალობის სტრატეგიის შესასწავლად. სწორედ ამიტომ თავიდანვე უნდა შეირჩეს ისეთი მოდელი, რომელიც კარგად ასახავს ადამიანში იგივე დაავადების მიმდინარეობას და პრევენციისა და მკურნალობის თაობაზე სწორი დასკვნების გაკეთების საშუალებას იძლევა.

საწყის ეტაპზე აუცილებელია გადავწყვიტოთ დიდ თუ მცირე ცხოველებზე ჩატარდება ექსპერიმენტები. ეს დამოკიდებულია კვლევის მიზნებსა და ამოცანებზე, ცხოველებთან მოპყრობის ეთიკურ საკითხებზე, კვლევის ხარჯებზე და პრაქტიკულ პირობებზე. ამიტომ თავიდან ცნობილი ცხოველური მოდელების დადებითი და უარყოფითი მხარეები უნდა შეფასდეს. სტატიაში დეტალურად არის განხილული არტერიული ჰიპერტენზიის ცხოველური მოდელები, რომლებიც ორ ძირითად ჯგუფად: პირველად და მეორად ჰიპერტენზიად შეიძლება დაიყოს. ესენციური ჰიპერტენზიის მოდელირებისთვის სამი ძირითადი მიდგომა არსებობს: ფარმაკოლოგიური, გარემო ფაქტორების ზემოქმედებით და გენეტიკური მოდელები. მეორადი ჰიპერტენზიის მიღება შესაძლებელია ფიზიკური მეთოდებით, როგორიცაა თირკმლის არტერიის კლიპირება ან მიკროემბოლიზაცია.

ALTERATIONS OF THE INTENSITY OF NEUN-IMMUNOREACTIVITY REACTIONS IN THE CEREBELLAR STRUCTURAL COMPONENTS OF RATS UNDER INFLUENCE OF THE FOOD ADDITIVES COMPLEX

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Currently, the quality of food is of particular value and is at the new level of review around the world. Every year, more and more people become attracted by a healthy diet as well as of the absence of a number of different additives in foods. However, the problem of a large number of food additives presence in the essential foods has not disappeared. For example, such synthetic dyes as E102, E110, E122, E124 are legal in Ukraine, while they have been banned for a long time in the EU and are included in the "Southampton list" [5].

We selected such food additives for our study as monosodium glutamate (food additive E621), ponso 4r (food additive E124) and yellow dye the 'sunset' (food additive E110).

The effects of various food additives, as well as of other substances on the cerebrum and the cerebellum, along with the response of various immunohistochemical markers were the subjects of the surveys of many authors. Morphological changes in the hippocampus of the offspring of rats after administration of PgE2 for labor stimulation were identified according to these studies, which correspond to changes in the brain during experimental fetal hypoxia [1], and there were also changes in the cerebellum: the thickness of the granular layer tended to thin down, a decrease in the number of cells of the granular layer per area unit, and an increase in the distance between Purkinje cells [2] Likewise, the study of the features of the GFAP and NeuN expression in the hippocampal formation of rat offspring after intravaginal administration of PgE2 to females for labor stimulation, demonstrated an increase of the relative area occupied by GFAP + astrocytes in comparison with the control, along with the gradual decrease of the relative area occupied by NeuN + neurons in contrast to the control animals [4]. After the administration of selected food additives complex, with the aid of the GFAP marker, the decrease in the average number of major neurons in the gray matter of the cerebellum was identified, which was the trigger for the reactive astrogliosis development and, accordingly, potential development of neuropathology [7].

In our study, we target to use the NeuN marker, to demonstrate changes in the structures of the cerebellum of rats under the influence of food additives complex.

Aim - to estimate the changes of the intensity of the NeuN-immunoreactivity reaction in the structural components of the cerebellum of rats under the influence of the food additives complex.

Material and methods. We used 100 white rats with an average weight of 258.1±0.67 g. in our study. The experiment was carried out on rats under normal conditions (group K - control) influenced by the complex of chemicals (monosodium glutamate, ponso 4r and the yellow dye the "sunset" (group E - experimental marked by the number of the week). Animals under the study as well as all manipulations on them were in accordance with the "Rules for the Use of Laboratory Experimental Animals" (2006, Appendix 4) and the Helsinki Declaration on the humane treatment of animals, in conformity with the Law of Ukraine "On the Protection of Animals from Cruel Treatment" (№. 3447-IV dated 02.21.2006) in compliance with the requirements of the Commission on Bioethics of the Ukrainian Medical Stomat ological Academy, in accordance with the provisions of the "European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes" (Strasbourg, 1986) [3,6].