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EXPERIMENTAL BRONCHIAL ASTHMA IN DIFFERENT LABORATORY ANIMAL MODELS (REVIEW ARTICLE)

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Abstract

The study of the mechanisms of allergic inflammation and airway hyper-responsiveness underlying bronchial asthma in animal experiments allows a deeper understanding of the mechanisms of these processes in humans. Therefore, experimental animals are widely used to study the physiology and pathophysiology of the respiratory tract, as well as research on the search for improved methods of treatment. In connection with this, today the relevance of this kind of work increases again due to the need to find pathogenetically justified methods of treatment of bronchial asthma.

In order to work on the development of a new formulation of allergy vaccine for subcutaneous allergen-specific immunotherapy, it is necessary to correctly determine the type of animal to model experimental bronchial asthma. For this purpose, a systematic search of scientific information was carried out about the specifics of modeling experimental bronchial asthma on different types of laboratory animals. To compile this review, a comprehensive search was conducted for publications in electronic databases: Pubmed, Scopus, Google Scholar, eLibrary. A number of experimental models of asthma in animals are described in the literature, which are used to study various aspects of pathogenesis and to test new ways of treating bronchial asthma. At the same time, each model has certain features that limit the scope of its use. Among large animals, rabbits, rhesus macaques, cats, dogs, horses, and sheep have been used to study allergies, since they are predisposed to develop allergic responses to antigens clinically relevant to humans. But most often mice and rats are used in modeling of the bronchial asthma. But every model has their own specific applications. This article describes the features of using different types of laboratory animals in modeling bronchial asthma.

Keywords: experimental bronchial asthma, animal modeling of asthma, sensitization, laboratory animals.

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Introduction. Bronchial asthma (BA) is the most common chronic disease worldwide, representing a significant social problem for both children and adults. The mechanisms of bronchospastic conditions and ways of their correction are actively studied all over the world, but the problem of BA remains far from being solved.

Allergen-specific immunotherapy (ASIT) is the only therapeutic approach capable of changing the natural course of the allergic process. The growth of allergic diseases and the small number of commercially available ASITs necessitates the search for new or improved allergy-specific therapies. And first of all, such research requires the proper modeling of allergic diseases on laboratory animals.

The main principle of modeling BA in animals consists in sensitization to an allergen with subsequent delivery of the causative allergen in different ways into the airways of sensitized animals, which leads to the development of a pathological process, immunological shifts and physiological features characteristic of human bronchial asthma. The basic criteria for the adequacy and reliability of the bronchial asthma model on animals to the parameters of the pathological process observed in humans with bronchial asthma. Obligatory criteria for animal models of BA: similarity with pathological processes occurring in humans, objective assessment of physiological parameters, reliability and reproducibility of the results.

The study of the mechanisms of allergic inflammation and airway hyperresponsiveness underlying BA in animal experiments allows a deeper understanding of the mechanisms of these processes in humans. Therefore, experimental animals are widely used to study the physiology and pathophysiology of the respiratory tract, as well as research on the search for improved methods of treatment.

In connection with this, today the relevance of this kind of work increases again due to the need to find pathogenetically justified methods of treatment of BA.

Aim: Systematic search of scientific information on experimental bronchial asthma in different models of laboratory animals.

Materials and methods. A comprehensive search of publications in electronic databases: Pubmed, Scopus, Google Scholar, eLIBRARY was performed to compile this review. A total of 148 literature sources were found, 51 articles were selected for analysis.

Exclusion criteria: publications outside the scope of this review; duplicate publications.

Sources were selected according to the base context of the study in English and Russian. Preference was given to publications in peer-reviewed journals. At the first stage, a general array of articles was selected, from which the most relevant ones were filtered according to keywords and context.

Inclusion criteria: Preference was given to articles of high methodological quality

Results. Studying the mechanisms of allergic inflammation and airway hyperresponsiveness underlying BA in animal experiments allows a deeper understanding of the mechanisms of these processes in humans. For this reason, experimental animals are widely used to study the physiology and pathophysiology of the respiratory tract, including the study of the cellular and humoral response to allergen administration.

ISSN 2524-0684 e-ISSN 2524-0692

The model of experimental BA using laboratory animals can act as an ideal tool to investigate and study the mechanisms that lead to asthmatic manifestations. Animal models are particularly useful to investigate various influences and to operate on already known processes to study their role and significance in the development of disorders that are characteristic of BA. There are many examples of processes described in animal models, and they are now crucial for the development and progression of the disease. A classic example is the determination of the role of Th1 and Th2 cells in allergic airway inflammation in animal models. These studies, using mice, determined the importance of Th2 cells in the progression of allergic disease and, in particular, the value of cytokines IL-4, IL-5, and IL-13, suggesting that allergic inflammation perpetuates and the development of increased airway reactivity [1].

If animal studies are able to figure out the mechanisms and characteristics of disease development, then it is possible to create and test drugs that act on certain links in order to prevent the development of the pathological process. In this regard, the use of animal models of asthma is a key link in conducting research in the search for and creation of drugs. But before a drug reaches the patient, it must undergo preclinical and clinical trials. However, preclinical and clinical trials for the vast majority of drug candidates are not only expensive but also unsafe. Therefore, prior to conducting these trials, it is necessary to screen drugs in order to select the most promising one.

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Using of animal models makes it possible not only to test the efficacy of a particular drug, but also to make an initial assessment of the drug's toxicity. The data obtained can subsequently be used as a starting point in deciding on the likelihood of clinical safety of the drug and the possibility of conducting preliminary trials of the drug on humans.

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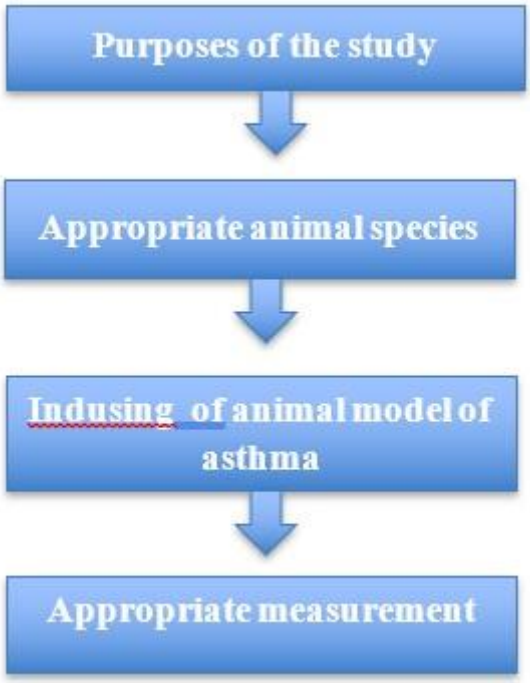

Figure 1 - Steps for inducing animal model of asthma

The literature describes a number of experimental models of BA in animals, which are used to study various aspects of pathogenesis and to test new ways of treating BA. At the same time, each model has certain characteristics that limit the scope of its use.

Mice. Mice have become the most popular in the modeling of allergic processes in the respiratory tract. In the literature, the most frequent data is that the modeling of BA in laboratory mice was initiated in 1994, when the first model of BA in linear mice was presented [2]. To date, there are a large number of protocols for modeling BA in mice. It has been proven that linear mice can be sensitized to various types of allergens and develop allergen-induced inflammation in the lungs [3,4]. The bronchial flush and lung tissue of model mice after allergen exposure contain eosinophils, macrophages, mast cells, and lymphocytes with Th2 phenotype [5,6]. A wide range of cytokines (IL-4, IL-5, IL-13, IL-9), activation products of mast cells and eosinophils are detected in lavage [7,8]. In mice with an allergic BA model, an overreaction is detected in response to the administration of methacholine and a causally significant allergen [9].

An important fact is that the mouse genome has been completely deciphered by now [10]. This makes it possible to use transgenic mice to study the molecular mechanisms of BA [11]. In addition, there is undeniable evidence of homology between the human and mouse immune systems, which makes mice desirable for studying the immune mechanisms of allergic and nonallergic BA [12,13]. Importantly for experimentalists, mice have a short reproductive cycle and are therefore more cost-effective for research. This fact also allows studies to begin more quickly after planning.

ISSN 2524-0684 e-ISSN 2524-0692

But despite the appeal of mice as biological objects for modeling BA, mouse models, as well as other animal models of BA, have their limitations [14]. One of the disadvantages of modeling BA in mice is that mice are suitable for modeling signs associated with asthma itself, rather than the whole phenomenon of asthma as a disease. According to the foreign literature, most research groups model allergic, in particular IgE-dependent BA in mice [15], although there are also works on modeling non-IgE-dependent BA [16].

According to international literature, BALB/c, C57BL/6, A/J, C3H/HeJ, SWR, FVR, DBA/2 mouse lines are more susceptible to sensitization and suitable for modeling allergic diseases [17]. Among the aforementioned lines, BALB/c and C57BL/6 are most commonly used to model IgE-dependent BA. BALB/c mice have been widely used to study induced bronchial hyper-responsiveness. They are characterized by high IgE- and IgGl- response to allergen administration, pronounced bronchial hyper-responsiveness to intravenous and inhalation administration of methacholine, and a significant number of eosinophils in bronchoalveolar lavage [18,19].

C57BL/6 mice are a less sensitized line than BALB/c. BALB/c and C57BL/6 differ genetically in the locus of the 11th chromosome that controls the amount of IL4 production by T cells; this region of chromosome corresponds to the 5q23-35 chromosome of humans [20]. The region contains a Th2 cytokine gene cluster, a Th2 cell response regulator, a T cell immunoglobulin domain, and a murine homologue of the hepatitis A receptor. It is important to note that most of the existing mouse lines with knockout specific genes used to study the molecular mechanisms of BA development are created using C57BL/6 [21]. Thus, the choice of a mouse line is an important factor in achieving the goals of the experiment.

In addition, it is important to remember that in order to obtain optimal immunological parameters (IgE/IgG1) and the response of the bronchial tract to the allergen, it is necessary to take young mice into the experiment, the optimal age of 8-12 weeks. At this age, mice are more susceptible to the effects on the respiratory and immune systems than adults [22].

One of the main drawbacks of BA models in mice is the lack of chronicity of the response to antigen exposure after sensitization [23]. If mice are sensitized with an antigen and then re-exposed to a permissive dose through the respiratory tract, they develop tolerance to the antigen after some time, resulting in a suppressed immunological response.

Given this peculiarity, it is not recommended to use the mouse model in order to study chronic processes in BA. But even in this issue, scientists are trying to find a solution to this issue. A regime has been proposed to simulate BA in mice that uses repeated inhalation of a low dose of allergen and as a result reproduces airway remodeling more similar to that observed in humans [24]. It has been shown that it is possible to induce a condition with manifestations similar to those in humans by sensitization and subsequent exposure through the airways to house dust, the allergen clinically most relevant to humans [25]. Such models are promising for research and may reduce some criticism of mouse models of BA.

ISSN 2524-0684 e-ISSN 2524-0692

Mice are and are likely to remain the most popular in BA modeling, if only because of their cost-effective conditions of use. They are an effective means of generating hypotheses for subsequent testing in humans.

Rats. Other popular animals for BA reproduction are rats. They, like mice, are relatively inexpensive, allowing large-scale studies sufficient to draw many conclusions. Historically, rats have been more popular in experimental research, until genetic technology was developed for use in studies performed on mice. Technically, rats have an advantage over mice in terms of their size. This makes it possible to extract material in quantities sufficient for studies, whether it is blood serum, bronchoalveolar fluid or respiratory tract tissue. All of this makes it much easier to obtain results using fewer animals. Compared to mice, the set of reagents available for studies in rats is significantly more limited, but recently the number of reagents has increased. But, with the development of transgenic technologies in rats, the number of studies on the mechanisms of allergy development in the rat model of BA may increase again [26].

For a long time, there was an opinion that it was impossible to model allergic processes and diseases in rats, in particular experimental BA. This point of view was disproved after the appearance of linear rats (Brown Norway, Wistar, Lewis). Subcutaneous sensitization of animals with a 1mg dose of ovalbumin or bovine serum albumin suspension with 200 μg aluminum hydroxide and intraperitoneal injection (1 ml) of inactivated pertussis vaccine followed by allergen inhalation on day 14-18 resulted in development of allergic inflammation in bronchi and their hyperresponsiveness, appearance of allergen-specific IgE-AT [27,28]. The same changes were observed in rats sensitized and subjected to allergen provocation according to the following protocol.

Rats were injected subcutaneously with a suspension of house dust (88 μg in protein) and aluminum hydroxide (150 μg), and inactivated pertussis vaccine (0.5 ml, concentration 1x109 microbial cells per 1 ml) was injected intraperitoneally. Fourteen days after subcutaneous injection, the animals were subjected to provocative intratracheal injection of 300 μl of physiological solution containing 17.6 μg of house dust. At present, a number of researchers abroad are actively using the abovementioned models of EBA in rats. Industrial allergens (e.g., toluene and methane derivatives) are also used to induce BA in rats [29].

As in the case of mice, the main criticism of rat models of BA is the tolerance that develops in response to prolonged allergen administration and the associated inability to achieve chronicity of the allergic response and changes in the lungs.

Rats are as easy to work with as mice. They are easy to sensitize and easy to induce an allergic response in the respiratory tract. In some ways they have an advantage over mice, but they also have their disadvantages. But it is impossible to refute the fact that rats have contributed to the development of an understanding of the mechanisms of bronchial asthma, as well as tolerance to allergens.

Guinea pigs. Guinea pigs have the longest history of being used in allergology. They have been used most extensively as a model to study contact hyperresponsiveness to chemical irritants and proteins.

ISSN 2524-0684 e-ISSN 2524-0692

Not without attention is the fact that many scientists involved in modeling bronchial asthma in animals note the marked adequacy of the guinea pig model of BA in humans [30,31]. Indeed, among laboratory animals guinea pigs are more susceptible to sensitization and develop bronchospasm after allergen inhalation. The difficulty of breathing in this species of animal increases within the next few minutes and the experimental individual dies of asphyxia. Autopsy of dead animals reveals severe pulmonary emphysema with areas of atelectasis, thick, viscous secretion with fibrinoid coagulation in the bronchial lumen. Histological examination reveals massive infiltration of the peribronchial tissue, interalveolar tissue and submucosa of the bronchi by eosinophils. There are a number of protocols for modeling BA in guinea pigs.

Hutson R. and colleagues developed a model of BA in which guinea pigs were sensitized and received provocative allergen injections by aerosol inhalation of ovalbumin [31]. E.S. Razovskaya and F.N. Shterenson [30] sensitized guinea pigs weighing 200-400 g by 3-fold subcutaneous injections of 0.2-0.4 ml of 25% egg protein suspension in physiological solution (intervals between injections were 3-4 days). After 14-21 days, the animals were placed in a chamber and exposed to aerosol from the same suspension. A few minutes after the start of inhalation, guinea pigs showed expiratory dyspnea. The difficulty in breathing increases over the next few minutes and, if contact with the antigen is not terminated, the animal dies in asphyxial convulsions. Repeated inhalation has no effect on surviving guinea pigs. At autopsy, severe emphysema with areas of atelectasis, thick, viscous secretion with fibrinoid coagulation in the bronchial lumen are observed. Histological examination reveals massive infiltration of peribronchial tissue, interalveolar septa and submucosa of bronchi with massive emphysema with atelectasis areas, thick, viscous secretion with fibrinoid coagulates in the bronchial lumen. Histological examination reveals massive infiltration of peribronchial tissue, interalveolar septa and submucosa of bronchi by eosinophils.

Histamine-induced BA has been developed using the guinea pig model. The development of this form of BA is induced only in guinea pigs. Inhalation by guinea pigs (especially by young individuals weighing 300÷350g) of a sprayed histamine solution (histamine concentration not less than 10-50 μg per 1 L of air) in 1-2 minutes causes bronchospasm phenomena extremely similar to asthma in sensitized animals. Despite the external similarity of "histamine" and allergic asthma, the pathomorphology of both are significantly different. Histamine-induced asthma is quite a suitable model for the search for means and methods of symptomatic treatment of BA in humans. Models of allergic asthma in guinea pigs have found their application and are indispensable in studying the mechanisms of early and late asthmatic response to an allergen in BA [32,33].

But even considering all the positive aspects, guinea pigs are less frequently used to study the pathogenesis of BA than mice and rats because of the lack of inbred lines and the small choice of specific reagents.

Use of large animals to model experimental bronchial asthma.

Among large animals, rabbits, rhesus macaques, cats, dogs, horses, and sheep have been used to study allergies, since they have a predisposition to develop allergic responses to antigens

ISSN 2524-0684 e-ISSN 2524-0692

clinically relevant to humans. The main problem with using these models is the difficulty and costliness of keeping them, as well as the almost no choice of specific reagents.

Rabbits. There are infrequent publications describing models of BA in rabbits. Periodic injections of allergen and adjuvant, starting from the neonatal period, followed by provocative injections of allergen in the form of aerosol, develop an inflammatory process, early and late phases of asthmatic response and bronchial hyper-responsiveness in the lungs of the animal. Initially, modeling was performed using Alternaría tenius [34], later the above technique was adapted to introduction of house dust and ragweed pollen.

A model of BA using a pneumocytotoxic serum was developed in rabbits. Donors of the serum are rats, and they are immunized with rabbit lung extract. A serum is obtained with a titer in the complement binding reaction: ++++ in a dilution of 1:80. The obtained serum is administered 6 times intravenously and twice in the form of aerosol inhalation at intervals of 3 days at a dose of 0.3 ml per 1 kg of animal weight. On histological examination of the lungs: small bronchi are spasmed, many lumens of alveoli are emphysematous, in some areas the tissue is in a state of hypoventilation or atelectasis. In some atelectatic areas there are focal hemorrhages and accumulation of leukocytes, mainly eosinophils. Interalveolar septa are thickened and infiltrated with histiocytes and eosinophils, many arterial walls are thickened [35].

Rabbit models of BA have been used to test traditional and genetically engineered drugs, inhaled forms of antireceptor drugs (e.g., against the adenosine Al receptor) [36]. The limited number of immunological reagents developed for this animal species and the low genetic homology of rabbits and humans has limited the use of these animals in biomedical research. Approaches to modeling the asthmatic response in this animal species have been able to become applicable to other, more suitable for modeling BA, animal species.

Rhesus macaques. About 25 years ago, Patterson R. and Harris K. started using rhesus macaques naturally sensitized to porcine ascarid antigens to study the allergen-induced early phase of the asthmatic airway response [37]. Skin sensitivity to a pure ascarid extract is determined in most primates living in the wild. This is probably due to prior sensitization to the parasite in primate habitats. Like most helminths, exposure to ascarid causes the primates to develop a Th2 response and increased IgE levels. Subsequent provocation of sensitized macaques with Ascaris suum extract leads to the development, early and late phase of the asthmatic response, which is accompanied by eosinophilia and hyper-responsiveness [38]. The model of BA using ascarid extract is attractive from the position that animals are sensitized to the parasite antigen in vivo, and this sensitization can be easily detected in the animal. Other models of BA developed in primates are induced using allergens relevant to humans, such as house dust, birch pollen (Bet VI, Bet V2) [38,39].

Sensitization of primates to pollen or household allergens for BA modeling is performed thoroughly, although there is data on spontaneous sensitization of nonhuman monkeys to house dust and cedar pollen [40]. An important advantage of models using pollen and household allergens is controlled and standardized sensitization to the causative allergen. The disadvantage

ISSN 2524-0684 e-ISSN 2524-0692

of protocols for modeling BA on primates is associated with a very labor-intensive work process and significant economic costs [41].

Cats. The report of "feline asthma" as a nosological form of mammalian disease appeared in the veterinary literature in the early 20th century, but it was not used as a model of BA until the end.

Padrride R. and colleagues described cats with increased mucus secretion, airway inflammation and clinical signs of difficult and wheezing breathing [42,43]. Along with the signs of chronic inflammation of the lower airways, cats showed increased pulmonary resistance, which disappeared after treatment with terbutaline, indicating the presence of reversible bronchospasm in sick animals. In addition, after exposure to low doses of methacholine, these cats developed bronchostenosis. For the first time, spontaneous hyper reduction was detected in the animals. These characteristics of "feline asthma" were equivalent to human BA symptoms. For research work, models of BA in cats were developed, useful for studying the mechanisms leading to airway pathology and for evaluating new therapeutic approaches to BA. One of the first allergens to model BA in cats was porcine ascarid antigen (Ascaris suum). Sensitization of healthy cats was performed by intramuscular injections. The animals were then subjected to inhalation of the antigen for 5 minutes for 3 times a week for 6 weeks while awake. As a result, pronounced respiratory eosinophilia and hypersensitivity to acetylcholine developed. In this model, serotonin was found to be a major mediator of mast cells in cats. The release of serotonin during mast cell degranulation causes bronchospasm in this species of animal. This mediator is absent in the airways of humans, horses, and dogs. Recent publications on modeling BA in cats are related to the use of house dust and pollen allergens as model allergens [44,45].

Dogs. Dogs have been also used as an anima model of asthma. It has been suggested that dogs represent an ideal model of allergy as they have a natural trait to develop allergic responses to antigens that are clinically significant to humans.This allergy usually manifests itself in superficial reactions in the form of dermatitis or conjunctivitis and reactions in the airways like asthma. Redman T. and colleagues developed a model of BA in dogs [46]. A specially bred breed of hound dogs characterized by high levels of total IgE and eosinophils in blood serum was used for modeling. Puppies of this breed were sensitized by intraperitoneal injections of ragweed pollen within 24h after birth and at 22 weeks of age. Fifty percent of the pups showed high levels of total IgE and blood eosinophilia. The animals were inhaled with ragweed pollen at intervals of 13 days, and after the third inhalation, carried out on day 45 from the time of the first inhalation, the puppies showed high levels of allergen-specific IgE- and IgG-ATs in their blood. Eosinophilia was detected in bronchoalveolar lavage, and histamine hyper responses were also detected and persisted for 5 months.

Models of allergic BA in dogs and cats are undoubtedly adequate for human BA, but their active use is limited by the lack of diagnostic capabilities to study the immunological mechanisms of the disease, as well as the high cost of biological objects [47].

Sheep. Sheep are an interesting subject for modeling respiratory diseases. In the foreign literature, there are a number of works devoted to the modeling of BA in sheep. The BA model is

ISSN 2524-0684 e-ISSN 2524-0692

induced by inhalation of various allergens, such as porcine ascarid antigen (Ascaris suum), ovalbumin, and house dust [48]. Prolonged inhalation delivery of the allergen (about 6 months) leads to airway remodeling. Pathological changes in the structure of bronchial tract have significant similarity with the pathomorphological picture of bronchi in human BA. Therefore, models of BA in sheep have found their application in the study of airway remodeling [49].

Horses. The "heavy breathing" syndrome is considered to be a naturally occurring disease of horses, similar to human BA [50]. Within this syndrome, acute bronchial obstruction, bronchial hyper-responsiveness and chronic airway inflammation develop. The "heavy breathing" syndrome diagnosed in horses is manifested by episodes of acute bronchial obstruction ("crisis"). "Crisis" develops in horses predisposed to developing the above syndrome within a few hours of exposure to moldy raw hay. In most cases, the antigens responsible for the development of hypersensitivity in horses are spores of Aspergillus fumigatus, Faenia rectivirgula, and Thermoactinomyces vulgaris.

Clinical remission in animals develops after elimination of provoking factors, when horses are transferred to special controlled housing. According to Robinson N. et al. the above syndrome is nothing other than chronic obstructive pulmonary disease in horses, so it cannot be considered an adequate model of human bronchial asthma [51].

Table 1 - The main discrepancies between the different kinds of animals used in animal models of bronchial asthma

Animal species	Advantages	Disadvantages
Mice	-low cost; -easily sensitized and challenged; -easy to handle; -reagents largely available -mice can be sensitized to various types of allergens and develop allergen-induced inflammation in the lungs; -the bronchial flush and lung tissue of model mice after allergen exposure contain eosinophils, macrophages, mast cells, and lymphocytes with Th2 phenotype -mice can be sensitized to various types of allergens and develop allergen-induced inflammation in the lungs; -indisputable evidence of homology between the human and mouse immune systems	-tolerance after repeated allergen exposure; - lack of chronicity of the response to allergen

ISSN 2524-0684 e-ISSN 2524-0692

Rat	-low cost; -easily sensitized and challenged; - larger than mice; -the possibility to take a larger volume of biomaterial than in mice	- tolerance after repeated allergen exposure; -reagents not easily available than reagents for mice; - harder to manipulate than mice
Guinea pig	-easily sensitized and challenged; -histamine-induced bronchial asthma; - more susceptible to sensitization and develop bronchospasm after allergen inhalation	-higher cost than mice and rat; - reagents not easily available; - tolerance after repeated allergen exposure; - the lack of inbred lines; -Axon reflex; -Limited genetic knowledge
Dog	-development allergic responses to clinically significant antigens to humans; - high levels of total IgE and eosinophils in blood serum; -development of long-term changes in pulmonary function; -natural susceptibility to allergens -large volume of biomaterial that can be taken for analysis	- high cost; -hard to manipulate; - expensive maintenance; -reagents not easily available; -larger airways (almost no bronchoconstriction)
Cat	-feline asthma -reversible bronchospasm with bronchodilators; -distal lung anatomy similar to human’s;	-high cost; -expensive maintenance; -hard to manipulate; -reagents not

	- high sensitivity to house dust and pollen allergens; - large volume of biomaterial that can be taken for analysis	easily available;

ISSN 2524-0684 e-ISSN 2524-0692

Rabbits	-often used for safety testing of biomedical drugs	-high cost; -hard to manipulate; -hard to manipulate; -reagents not easily available; -low genetic homology of rabbits and humans
Sheep	-immediate physiological responses to inhaled allergen; -prolonged airway hyperresponsiveness after challenge; - large volume of biomaterial that can be taken for analysis	-high cost; -expensive maintenance; -hard to manipulate; - reagents not easily available; -very labor-intensive work process; -platelet factor antagonists modulate the late-phase allergic response in sheep but not in humans
Horse	-"heavy breathing" syndrome; -sensitivity to fungal allergens -large volume of biomaterial that can be taken for analysis	-high cost; -expensive maintenance; -hard to manipulate; - very labor-intensive work process; -most often neutrophilic inflammation -reagents not easily available; -it is most often used for chronic obstructive pulmonary disease;
Rhesus	- lung anatomy similar to human’s;	-high cost;

ISSN 2524-0684 e-ISSN 2524-0692

macaques	-large volume of biomaterial that can be taken for analysis - sensitization to parasite antigens (Ascaris suum)	- expensive maintenance; -hard to manipulate; -very labor-intensive work process;

There is a huge amount of literature concerning the description of models of bronchial asthma in animals, including methods and variations of reproduction [1]. Ovalbumin is most commonly used as an antigen in animal experiments, including mice, rats and guinea pigs [11]. Animals are usually sensitized by intraperitoneal injection of ovalbumin with adjuvant [13]. Intraperitoneal injections of the antigen may be single or followed by additional injections, usually two weeks later, of ovalbumin aerosol. With this method, a picture develops in the airways that has some resemblance to the inflammatory component of asthma.

Aluminum hydroxide, which predisposes the immune system to develop a Th2 cell response, is used more often as an adjuvant [3]. The problem with using adjuvants is that they can alter the process of modeling sensitization by an allergen, leading to an even greater difference from the processes occurring in the human body. Models have been developed that do not require the use of adjuvants to reproduce. For example, by intranasal administration of the allergen into A/J mice. Asthmatic-like changes in the lungs were noted. The method was assumed to have an advantage over others, since the effect was through the organs affected in BA, rather than affecting the immune system as a whole [7]. However, the use of this method was limited to mice of a particular line, and the BALB/c and C57BL/6 mice more commonly used in experiments showed a weaker response when exposed in this way than when classical intraperitoneal sensitization with ovalbumin was used [20]. Most animal models of BA lack the chronic manifestations characteristic of the disease and prolonged airway hyper-responsiveness [14]. In fact, most models known to date are models of acute inflammation. Moreover, it is well known that mice, rats and guinea pigs sensitized with a particular antigen become tolerant to it over time [2, 13]. That is, due to peculiarities of their physiology, animals adapt to chronic exposure and stop reacting the way experimenters would like them to. But this phenomenon is also of interest for researchers, because finding out the mechanism of tolerance development to the antigen under chronic exposure could become the basis for the development of means and methods of formation of such resistance in humans.

Conclusion. Finding new treatment strategies for patients with allergies is a major public health problem. Because allergic conditions often lead to a decrease in the quality of life of patients, interruptions in work and possibly loss of employment, which in turn leads to financial losses not only for the patient or the employer, but also for the state as a whole.

Today, ASIT is the only one capable of changing the body's relationship to an allergen and preventing the further development of allergies. For this reason, the relevance of works to search for new directions in research of BA pathogenesis and search for pathogenetically

ISSN 2524-0684 e-ISSN 2524-0692

grounded methods of treatment is increasing again, which, in its turn, requires research on laboratory animals.

The literature describes a number of experimental models of BA in animals, which are used to study various aspects of pathogenesis and approve new methods of BA treatment. At the same time, each model has certain characteristics that limit the scope of its use.

Among large animals, rabbits, rhesus macaques, cats, dogs, horses, and sheep have been used to study allergies, since they have a predisposition to develop allergic responses to antigens clinically relevant to humans. But the main problem with using these models is the difficulty and costliness of keeping them, as well as the almost zero choice of specific reagents.

Guinea pigs have the longest history of use in allergology. They have been used most extensively as a model to study contact hyper-responsiveness to chemical irritants and proteins. Among laboratory animals, guinea pigs are more susceptible to sensitization and develop bronchospasm after allergen inhalation. But even considering all the positive aspects, guinea pigs are less frequently used to study the pathogenesis of BA than mice and rats, also because of the lack of inbred lines and the small choice of specific reagents.

Analysis of the literature and studies on the modeling of BA on animals leads to the conclusion that laboratory mice and rats are most often used in the modeling of BA.

From a technical point of view, rats have an advantage over mice with regard to their size. This makes it possible to obtain material in quantities sufficient for studies, whether it is blood serum, bronchoalveolar fluid or respiratory tract tissue. All of this makes it much easier to obtain results using fewer animals. Compared to mice, the set of reagents available for studies in rats is significantly more limited, but recently their number has been steadily increasing.

The main criticism of rat models of BA is the tolerance that develops in response to prolonged allergen administration, and the associated inability to achieve chronicity of the allergic response and changes in the lungs.

Rats, just like mice, are easy to work with. They are easy to sensitize, they are easy to induce an allergic reaction in the respiratory tract. In some ways they have an advantage over mice, but they also share their disadvantages. They have contributed to the development of an understanding of the mechanisms of bronchial asthma, as well as tolerance to allergens.

Mice have become the most popular in modeling allergic processes in the respiratory tract. It has been proved that linear mice can be sensitized to various types of allergens and develop allergen-induced inflammation in the lungs. Another important fact is that the mouse genome has been completely deciphered by now [10]. This makes it possible to use transgenic mice to study the molecular mechanisms of BA development [11]. In addition, there is undeniable evidence of homology between the human and mouse immune systems, which makes mice attractive for studying the immune mechanisms of allergic and nonallergic BA [12,13].

As in the case of rats, one of the disadvantages of mouse models of BA is the lack of chronicization of the response to antigen exposure after sensitization [23]. If mice are sensitized with an antigen and then re-exposed to a permissive dose through the respiratory tract, they develop tolerance to the antigen after some time, resulting in suppression of the immunological

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response. Given this peculiarity, it is not recommended to use the mouse model when studying chronic processes in BA. But even in this issue, scientists are trying to find a solution to this issue. They have proposed a regime for simulating BA in mice that uses repeated inhalation of a low dose of allergen and reproduces airway remodeling that is more similar to that observed in human BA.

Mice are and are likely to remain the most popular in BA modeling, if only because of the cost-effective conditions of their use. This is due to a number of reasons: mice have a short reproductive cycle, which allows a quicker start of research after planning; lower maintenance costs compared to other types of laboratory animals; and the fact that mice are physically more convenient to use in research due to their low body weight and diminutiveness, and they are less aggressive than rats is also important for experimenters. And one cannot ignore the fact that, historically, mice have been an effective means of generating hypotheses for subsequent testing in humans.

SPF status (Specific Pathogen Free) is an important component of animal research, regardless of species. SPF status makes it possible to conduct research at the state-of-the-art level and obtain reproducible results.

Each type of laboratory animal in BA modeling has its own advantages and disadvantages. But it must be remembered that the choice of laboratory animal in BA modeling depends primarily on the purpose of the study. With the right choice of laboratory animal and a good study design, there will be good reproducible results that can be published in international peer-reviewed journals.

Currently, the work is continuing on the creation of effective and safe forms of modified ASIT. The use of experimental models of experimental BA can make a significant contribution to a comprehensive assessment of the impact of the therapeutic agents being developed on the experimental allergic process, which could be the basis for recommending new forms of ASIT for clinical trials and further implementation in practical healthcare. But to achieve these goals, the choice of the laboratory animal in the simulation of BA is very important. If the right animal species for BA modeling is chosen for the purpose of the study, reliable reproducible published results can be obtained, which can serve as a basis for other studies.

Conflict of interest

The authors of the article confirmed that there is no conflict of interest to be reported.

Authors' contribution

All authors contributed equally to the conception, execution, processing of the results, and writing of the article. We declare that this material has not been previously published and is not under consideration by other publishers.

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ӘРТҮРЛІ ЗЕРТХАНАЛЫҚ ЖАНУАРЛАР МОДЕЛІНДЕГІ ЭКСПЕРИМЕНТАЛДЫ БРОНХИАЛДЫ ДЕМІКПЕ

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Түйіндеме

Аллергиялық қабыну механизмдерін және бронхиалды демікпе негізіндегі тыныс алу жолдарының гиперреактивтілігін жануарларда жүргізілген экспериментте зерттеу арқылы адамдардағы осы процестердің механизмдерін тереңірек түсінуге мүмкіндік береді. Сондықтан да эксперименталды жануарлар тыныс алу жолдарының физиологиясы мен патофизиологиясын зерттеу үшін, сондай-ақ жетілдірілген емдеу әдістерін іздеу үшін кеңінен қолданылады.

Ірі жануарлардың арасында аллергияны зерттеу үшін қояндар, резус макакалары, мысықтар, иттер, жылқылар мен қойлар пайдаланылды, өйткені олар адамдар үшін клиникалық маңызды антигендерге аллергиялық реакциялардың дамуына бейім. Бірақ көбінесе бронх демікпесін модельдеу кезінде тышқандар мен егеуқұйрықтар

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қолданылады. Бірақ әрбір лабораторлық жануардың бронх демікпесін модельдеуде өз қолдану ерекшеліктері де бар.

Бұл мақалада бронхиалды демікпені модельдеу кезіндегі зертханалық жануарлардың әртүрлі түрлерін қолдану ерекшеліктері сипатталған.

Түйін сөздер: эксперименттік бронх демікпесі, жануарларға демікпені модельдеу, сенсибилизация, зертханалық жануарлар.

ЭКСПЕРИМЕНТАЛЬНАЯ БРОНХИАЛЬНАЯ АСТМА НА РАЗНЫХ МОДЕЛЯХ ЛАБОРАТОРНЫХ ЖИВОТНЫХ (ОБЗОРНАЯ СТАТЬЯ)

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Аннотация

Изучение механизмов аллергического воспаления и гиперреактивности дыхательных путей, лежащих в основе бронхиальной астмы, в эксперименте на животных позволяет глубже понять механизмы этих процессов у человека. Поэтому экспериментальные животные широко используются для изучения физиологии и патофизиологии дыхательных путей, а также исследование по поиску усовершенственных методов лечения. Связи с этим, на сегодняшний день актуальность такого рода работ вновь возрастает в связи с необходимостью поиска патогенетически обоснованных методов лечения бронхиальной астмы.

Среди крупных животных для изучения аллергии использовались кролики, резус-макаки, кошки, собаки, лошади и овцы, так как они имеют предрасположенность к развитию аллергических ответов на антигены, клинически значимые для человека. Но чаще всего при моделировании бронхиальной астмы используются мыши и крысы. Важно помнить, что каждая модель имеет свои особенности применения при моделировании бронхиальной астмы.

В данной статье описаны особенности использования разных видов лабораторных животных при моделировании бронхиальной астмы.

Ключевые слова: экспериментальная бронхиальная астма, моделирование астмы на животных, сенсибилизация, лабораторные животные.