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Application of experimental simulation when studying the pathogenesis of osteoarthrosis

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Abstract. Osteoarthritis is a chronic degenerative-inflammatory disease of the joints, which is accompanied by the destruction of articular cartilage, leading to dysfunction and, in the later stages, the appearance of contractures, muscle atrophy and skeletal deformities. The main clinical manifestations of osteoarthritis are chronic pain of varying intensity and limitation of joint mobility, which significantly impairs the quality of life of patients. Modern research indicates the multifactorial nature of the development of osteoarthritis. With the development of the disease, significant changes occur at all levels of the organization, including changes in molecular processes in the cartilage, accompanied by violations of its structure and functional properties, as well as the regulation of the synthesis of components of the cartilage matrix by chondrocytes. The study of the pathogenesis of osteoarthritis was the basis for the development of new drugs. The problem of the reliability of alternative modeling, efficacy, bioequivalence or toxicity of substances for humans requires their complete validation and qualitative verification using animal models. The purpose of this review is a comparative description of in vivo and in vitro experimental models used to study the pathological processes of osteoarthritis, and an analysis of the limits of their applicability.

Key words: osteoarthritis, articular cartilage, experimental modeling, in vivo models, in vitro models, cell culture.

Modeling is an effective tool for analysis and forecasting in various applied research. Today it is difficult to imagine research and design activities without the use of methodology and modern modeling tools. A model is a material or mentally imagined object that, in the process of research, replaces the object - the original, while retaining all its important properties for this research [1-15]. The most common

motive for building a model of a complex dynamic system is to predict the future behavior of this system. Using the model as an example, it is possible to work out an algorithm for the control and regulation of a certain process [14-20].

Experimental modeling of pathological processes plays an important role in studying the mechanisms of development of various diseases [24-29]. This method is key in the research work of morphologists and clinicians. There are no formal techniques for creating adequate models. The final judgment about the suitability of the model is given by practice, i.e. comparison of the model with the original object [4]. To analyze the adequacy of the experimental models of osteoarthritis (OA) presented in this review, the pathogenesis of this disease is described below [21, 22, 23, 30-37].

Advantages and disadvantages of animal and cellular models of OA. Due to insufficient knowledge of the factors of the pathogenesis of OA, its animal models can be used to study parameters that are not available in the study of the in vitro system (distribution in organs and tissues, excretion from the body, metabolism, etc.). In vitro systems can be used as indicators of toxicity and to study mechanotransduction [38-42]. Extrapolation of the obtained results to a person is an obligatory, complex and controversial stage of any experimental modeling. The most complete principles of extrapolation have been developed in the field of assessment of acute and chronic toxicity of substances in laboratory animals. Either direct transfer of data from animals to humans is used, or correction factors are introduced. In vitro models can more or less fully represent the facets of the display from the molecular to the cellular level as much as possible. When extrapolating data from in vitro biotesting models to humans, a high sensitivity of biotest objects to substances is noted [43, 44, 47, 49, 55].

The main advantage of using in vitro systems is obtaining scientifically grounded results that can be applied not only in practice, but also in the development of fundamental research. In addition, the use of in vitro methods is an ideal way to

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quickly and inexpensively obtain accurate results, bypassing the stage of experiments on laboratory animals, which allows you to comply with ethical standards [45, 46, 47, 50, 51-54]. The disadvantages of in vitro models include their inadequacy for assessing risks for subsequent generations of cells or the whole organism [55-63]. Undoubtedly, the choice of a model should be determined by the tasks of a particular experiment.

Prospects for in vivo and in vitro modeling. Despite the development of new modeling methods, it is impossible to completely abandon testing on experimental animals. The use of animals in medicine is one of the important problems in bioethics. When developing new in vivo models of OA and using new in vivo models in scientific research described in the literature, it is necessary, first of all, to be guided by international documents regulating experiments and studies on animals. In practice, most of them are experimental animals.

A variety of methods for modeling experimental OA in animals indicates the need to obtain models corresponding to different stages of deforming arthrosis in sick patients. Macroscopic and morphological changes in the joint should correspond to the early (I and II) stages of arthrosis in humans for testing drugs intended for the conservative treatment of OA. To obtain the initial degenerative processes in the joint, it is necessary to provide not an acute surgical, but a long, gradually progressive discrepancy between the real and proper levels of its structures [9]. Simulation of experimental OA in animals allows one to take into account the multifactorial nature of this disease, as well as to manage some modeling criteria, such as biomechanical load, period and degree of immobilization. Prospects for the development of in vivo modeling of OA are to improve the quality of animal maintenance - to create GLP vivariums not only for small laboratory animals (rats, mice, hamsters), but also for large ones (rabbits, mongrel dogs). In accordance with the main provisions of the recommendations for conducting biomedical research using animals, it is necessary to minimize the number of animals used in modeling [64, 67].

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The wide variety of cell models indicates the absence of adequate in vitro systems for which direct extrapolation of data to humans is impossible. Further development of cell modeling is aimed at developing three-dimensional models that take into account not only the effect of cytokines and osmotic pressure, but also the morphological structure, location of chondrocytes in the cartilage [65, 66]. The structural features of the multicomponent extracellular matrix of cartilage allow it to withstand high biomechanical loads. For the formation of such an organization in vitro, conditions are necessary, including certain mechanical influences, which can be provided only in the above-mentioned specialized devices - bioreactors [2, 36].

The multifactorial nature of OA should be considered when designing a model for disease reproduction, even if it is only testing one parameter, such as response to exercise or catabolic stimulus [1]. When planning a study, to assess the effectiveness of therapy, it is necessary to use a model (or several models) that most closely matches the objectives of the study. Therefore, at present, for the most comprehensive study of the mechanisms of reproduction of the disease and the effect on its course, various types of both in vitro and in vivo models should be used.

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