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Modern approaches to modeling *in vivo* degenerative spine diseases

V. O. Radchenko [1], M. A. Skidanov [1], N. O. Ashukina [1], V. Ye. Maltseva [1], A. G. Skidanov [1, 2], O. O. Barkov [1]

[1] Sytenko Institute of Spine and Joint Pathology National Academy of Medical Sciences of Ukraine, Kharkiv
[2] Municipal non-profit enterprise «City Multidisciplinary Hospital No. 18» of the Kharkiv City Council.Ukraine

Every year, more and more people suffer from illnesses and disabilities that occur due to lumbar pain. Many studies, some of that use in-vivo models, are conducted to decrease the socioeconomic impact of the consequences of degenerative spine diseases. Objective. To evaluate the advantages and disadvantages of different in vivo models that are used to study the mechanisms of development of degenerative disturbances in spinal motion segments and test prospective methods of treating them. Methods. A search was conducted in the PubMed, Google Scholar, and Base scientific databases with the following key words: Spinal Diseases, Spine Disorder, Intervertebral Disc Degeneration (Repair), Facet Joint Degeneration (Repair), Animal Model, Facet (Zygapophyseal) Joint Osteoarthritis, Canine (dog), Swine (Pig), Ovine (sheep), Rabbit, Rat, Mice. The depth of the search was 10 years. Results. Rodents, pigs, goats, dogs, sheep, and primates are used to study mechanisms of development of degenerative disturbances in spinal motion segments and to test different approaches. Studies on larger animals are conducted due to their similarities in size, anatomy, biomechanics, and histological structure of vertebrae and intervertebral discs to humans. Models using dogs and alpacas are specifically of interest because of the natural age-related degradation of their intervertebral discs. However, experiments using large animals are restricted by high costs and bioethics regulations. The use of rabbits, rats, and mice in experiments is promising. For these animals, degenerative disturbances in the spine are modeled by creating traumatic injuries (disturbing the integrity of facet joints, endplates, annulus fibrosus, and nucleus pulposus, nucleotomy, and discectomy) or injection of chemical agents. Conclusions. The advantages of using of rodents instead of large animals to model the mechanisms of development of degenerative spine diseases and to test treatment methods include the relative ease of use and reproducibility of experiments, and economic and ethical viability. However, models should be chosen carefully and according to with the aims of the study.

Поширеність захворюваності й інвалідності через поперековий біль у світі постійно зростають. Для зменшення соціально-економічних наслідків дегенеративних захворювань хребта проводять масштабні дослідження, зокрема, із використанням моделей in vivo. Мета. З'ясувати переваги та недоліки різних експериментальних моделей in vivo для вивчення механізмів розвитку дегенеративних порушень у складових хребтових рухових сегментах і тестування методик їхнього лікування. Методи. Проведено пошук джерел літератури в наукових базах PubMed, Google Scholar, Base за ключовими словами Spinal Diseases, Spine Disorder, Intervertebral Disc Degeneration (Repair), Facet Joint Degeneration (Repair), Animal Model, Facet (Zygapophyseal) Joint Osteoarthritis, Canine (dog), Swine (Pig), Ovine (sheep), Rabbit, Rat, Mice. Глибина пошуку прийнята 10 років. Результати. Для вивчення механізмів розвитку дегенеративних порушень у хребтових рухових сегментах або випробовування лікувальних стратегій використовують лабораторних гризунів, свиней, кіз, собак, овець, приматів. Дослідження на великих тваринах виконують завдяки порівнянним розмірам, анатомії, біомеханіці та гістологічній структурі тіл хребців і міжхребцевих дисків. Через природну дегенерацію з віком привабливими для вивчення механізмів розвитку дегенеративних захворювань хребта є моделі на собаках та альпаках. Проте експерименти на великих тваринах обмежені високою вартістю та вимогами біоетики. Перспективним є використання кролів, щурів, мишей. У них дегенеративні зміни у хребті моделюють шляхом виконання травматичних ушкоджень (порушення цілісності дуговідросткових суглобів, замикальних пластинок, волокнистого кільця чи драглистого ядра, нуклеотомії, дискектомії) і введення хімічних агентів. Висновки. Перевагою лабораторних гризунів перед великими тваринами в якості моделей для вивчення механізмів розвитку дегенеративних захворювань хребта і тестування методик їхнього лікування є простота застосування та легкість відтворювання, економічна й етична виправданість. Проте обирати модель необхідно ретельно відповідно до завдань дослідження.

Ключові слова. Моделі тварин, дегенерація міжхребцевого диска, остеоартроз дуговідросткових суглобів, щур.

Key words. Animal models, intervertebral disc degeneration, osteoarthritis of facet joints, rat

Introduction

Humans are representatives of the animal kingdom; accordingly, they obey the same physical and chemical laws. The laws of Mendel and molecular genetics that determine our heredity are valid for all living organisms. Finally, the basic biological processes collectively known as «life» are common to all animal species. For example, the mechanisms of heart rhythm generation in humans do not fundamentally differ from those of fish, frogs, snakes, birds or monkeys. The molecular and electrical basis of nerve impulse formation and transmission are the same in the human brain and the nerve fibers of squid, crabs, or rats. Much of what we know today about the functioning of human cells, tissues, and organs was first discovered in the process of research on various vertebrates and invertebrates [1].

Historically, to understand the features of the spine under in development of degenerative disorders in the components of the spinal motor segments or in the process of aging, to develop treatment strategies, experimental modeling on animals is used [2–4]. *In vivo* models make it possible to expand knowledge about individual links of the degenerative process, to investigate the mechanisms of its development based on the study of structural features of spinal motor segments, metabolic and molecular indicators [5]. It is rather difficult to study these issues in humans due to the small amount of material and, especially, the impossibility of obtaining intact tissues for analysis. Usually, experiments reproduce degeneration of the intervertebral disc [6, 7] and osteoarthritis (OA) of the arcuate joints [8, 9]. This is due to the fact that the specified abnormal conditions trigger back pain, which is the leading cause of disability in the world [10]. Over the past 20 years, the incidence, prevalence, and disability rates due to low back pain have increased by ~50 %. In addition, the risk of low back pain increases in direct proportion with the aging of the population of the globe and the socio-demographic index (more than 3 times higher in countries with a high index than with a low one). It is predicted that the incidence, prevalence of low back pain and disability due to it will increase approximately 1.4 times by 2050 [11]. In order to reduce the socio-economic consequences of degenerative diseases of the spine, large-scale research is ongoing in the world, in particular, using *in vivo* models.

Purpose: to find out the advantages and disadvantages of various *in vivo* experimental models for studying the mechanisms of the development of degenerative disorders in the constituent spinal motor segments and testing the methods of their treatment.

Material and methods

Literature sources were searched in scientific databases PubMed, Google Scholar, Base using the keywords «Spinal Diseases», «Spine Disorder», «Intervertebral Disc Degeneration (Repair)», «Facet Joint Degeneration (Repair)», «Animal Model», «Facet (Zygapophyseal) Joint Osteoarthritis», «Canine (dog)», «Swine (Pig)», «Ovine (sheep)», «Rabbit», «Rat», «Mice». The search depth was 10 years.

Results and their discussion

Today, there are many models using different species of animals, which were created to study the development of degenerative changes in the spine and to substantiate the methods of their treatment.

Models on large animals

Large animals, dogs, goats, pigs, and sheep are most often used to model degenerative diseases of the spine [12].

Experimental studies on pigs are performed due to the relative similarity of the size and geometry of the vertebrae: the length of the transverse process, the distance between the arcuate joints, the angle of inclination of the vertebral leg, the depth of the vertebral body, the diameter and shape of the leg [13]. It has been proven that in terms of anatomical and morphological features, the cervical spine of a pig is comparable to that of a human and can be used in *in vivo* studies [14]. Similar changes were also found in the intervertebral discs of humans and pigs during aging, namely: an increase in the expression level of matrix metalloproteinase-1 (MMP-1) against a background of reduced expression of type II collagen and aggrecan, a decrease in the number of cells and glycosaminoglycan (GAG) molecules, an increase the ratio of GAG to the number of cells [15].

The authors believe that the pig model is adequate for studying age-related changes in the metabolism of the intervertebral disc, as well as for testing hypotheses about degenerative processes in it in real time. A classic model of degenerative disorders in the intervertebral disc in pigs for further research into its regeneration strategies is nucleotomy [16], traumatic injury of the annulus fibrosus [17, 18] or the locking plate and their various modifications. In particular, a model of cryoinjury of the pig disc, performed through the perforation of the locking plate, was proposed, the relevance of which for obtaining disc degeneration was proven histologically [19]. Also, the development of degenerative disorders in

the intervertebral disc of sexually immature pigs was provoked by disrupting nutrition through the locking plates by blocking them with bone cement, according to the type of balloon kyphoplasty. Based on the study of the signal on T2-weighted MRI images and histological analysis, destructive changes in the gelatinous nucleus and fibrous annulus were determined [20]. A similar model was later developed and validated for the lumbar spine of a goat [21].

Recently, it has been proposed to use the cervical spine of alpacas as a potential model for studying degeneration of the intervertebral disc due to its human-like location and biomechanical properties, the size of the intervertebral discs, and their natural age-related impairment [22].

To simulate degenerative changes in the intervertebral disc, sheep were subjected to nucleotomy from the posterolateral approach at three levels of the lumbar spine and 6 months after that, with the help of radiography and MRI, a decrease in the disc height index and disc height was determined [23]. Mature sheep were used to create a new model of degeneration of the intervertebral discs at the level of the lumbar spine without damage to the annulus fibrosus. For this, a tunnel with a diameter of 2 mm was formed in the locking plate through a transpedicular approach and a partial nucleotomy was performed. With the help of x-ray, MRI and histology methods, the progression of disc degeneration has been proven for periods of 1, 3, 6 months and the model is recognized as suitable for studying the latest strategies for restoring the gelatinous nucleus [24].

The first reports of intervertebral disc herniation in dogs appeared in the 1800s, and these animals were found to have degenerative diseases of the spine, which means that they can be used in the study of these abnormalities [25]. According to the results of the review of modern peer-reviewed special publications, it is known that the important anatomical, physiological, histological and molecular features of spinal diseases are similar for dogs and humans [26]. In particular, due to degenerative changes in the intervertebral disc, dogs experience back pain, so they are diagnosed and treated for this impairment. It is known that presentation, macroscopic and microscopic features of degeneration of the intervertebral disc are similar in humans and dogs. In both, decompression and spondylodesis operations are often used to treat degenerative diseases of the spine [7, 27]. Spontaneous spondylomyelopathy, stenosis of the spinal canal [26, 28, 29], and osteoarthritis of the arcuate joints [29] are also observed in dogs. An important feature of this animal species is the decrease in the number of notochordal cells from birth and their complete loss by adulthood, which is a factor in the development of degenerative diseases of the spine [6]. Dogs are divided into chondrodystrophic (CD) and non-chondrodystrophic (NCD) breeds. The former develop short, arched limbs and degenerative diseases of the intervertebral disc before the age of 1 year due to a violation of the endochondral ossification of long bones. In NCD breeds, the spontaneous development of disorder is observed at 5–7 years of age. As in humans, in CD and NCD dogs, with increasing severity of the disease, the relative content of GAG decreases in the affected intervertebral discs, the activity of MMP-2 increases [7], the levels of inflammatory mediators, namely prostaglandin E2 and cyclooxygenase-2 (in the gelatinous nucleus) [30]. Degeneration of the intervertebral disc in dogs of both breeds occurs according to the type of chondroid metaplasia of the gelatinous nucleus [30].

All of the above makes dogs a good model for studying the mechanisms of development of degenerative diseases of the spine during life. Lately, dogs have been rarely used for *in vivo* modeling of abnormal conditions in the constituent spinal motor segments; usually, a discectomy is performed for this purpose [31, 32].

Thus, studies on large animals are performed due to the comparable size, anatomy, biomechanics and histological structure of the vertebral bodies and intervertebral discs. Due to natural degeneration with age, dog and alpaca models are preferable for studying the mechanisms of development of degenerative spine diseases. However, the use of large animals in experiments is quite costly and difficult from the point of view of modern ethical norms, therefore a significant number of *in vivo* models have been developed for rodents — rabbits, rats, and mice. These animals quickly reproduce and reach sexual maturity, are easy to use and model various abnormal conditions, in particular, with the use of genetic technologies.

Rodent models (rabbits, rats, mice)

To determine the therapeutic effect of cultured mesenchymal stromal cells of bone marrow and chondrocytes, a model of degeneration of the intervertebral discs of the lumbar spine of rabbits was developed, which involved piercing the annulus fibrosus with a needle and simultaneous aspiration of the gelatinous nucleus. The model was validated using MRI, biomechanical tests of discs with determination of compressive strength and modulus of elasticity, analysis of type II collagen content [33]. The rabbit intervertebral disc puncture model at the level of the lumbar spine was used to study the therapeutic

effect of hyaluronic acid [34]. Simultaneous puncture of the lumbar intervertebral disc of rabbits with sodium iodoacetate (0.01, 0.1, or 1 mg) causes death of notochordal cells and a gradual decrease in disc height in a dose-dependent manner from 2 to 12 weeks [35]. One of the puncture models recommended by the authors to study regeneration with the introduction of biomaterials into the intervertebral disc after its degeneration is percutaneous posterolateral disc puncture with/without aspiration of the gelatinous nucleus [36].

To study the effect of spondylodesis on the level of pro-inflammatory cytokines in the intervertebral discs, a suitable rabbit model was developed. For this, disc degeneration was reproduced by puncture, and for fusion, posterior or posterolateral decortication was performed using autografts from the iliac bone [37]. This model is also used to analyze the structure of the intervertebral discs adjacent to the spondylodesis site. In this case, interbody spondylodesis in the lumbar spine is performed after the puncture of the intervertebral disc and the occurrence of degeneration in it [38].

Recently, it has been established that in rabbits with a knockout of the apolipoprotein E gene (a protein that is responsible for the transport of lipids between cells of various tissues), nutrition of the intervertebral disc is disturbed, with subsequent cell death and premature degeneration in it. The authors determined that this process, as in humans, is associated with the accumulation of inflammatory factors (interleukin-1β, tumor necrosis factor-α, ADAMTS-4, ADAMTS-5 and MMP-3). Therefore, they suggest using apolipoprotein E gene knockout rabbits as a model for preclinical trials of drugs intended for the treatment of degenerative disorders in the intervertebral disc [39].

To study the effect of decompression spondylodesis in the cervical spine on adjacent intervertebral discs, some authors suggest modeling instability in rabbits by nucleotomy with partial destruction of the annulus fibrosus [40].

For the study of degenerative changes in spinal motor segments in an experiment on rats, an important aspect is the understanding of the similarity of the development of degenerative processes in these animals and humans. Computer microtomography showed that the vertebrae of the cervical and lumbar spine of rats have a comparable morphology to the human vertebrae in the axial plane. Based on this, the authors consider it possible to use these animals for biomechanical studies on the spine [41]. To study age-related degenerative changes in the lumbar and cervical spine, sand rats are used, in which disc degeneration occurs spontaneously with age. Using the methods of histology and radiography, it was established that at the level of the cervical and lumbar spine these animals, with age, undergo narrowing of the intervertebral space, formation of osteophytes, calcification of the locking plates, unevenness of the edges, and extrusion of herniated intervertebral discs. Identified impairments were more severe in the cervical spine [42]. Also cervical and lumbar intervertebral discs of sand rats older than 9 months were found to have degenerative changes in the gelatinous nucleus and ruptures in the annulus fibrosus, which morphologically corresponded to those in humans [43].

The authors concluded that the model was suitable and economically justified for the study of spontaneous degeneration of intervertebral discs in the aging process.

Since rats are quite often used to model degenerative changes and develop approaches to optimize the regeneration of the intervertebral disc, on the initiative of the members of the spine section of the Orthopedic Research Society (ORS), a standardized system for histological evaluation of the degeneration of this structure was developed and a protocol for the preparation of material for analysis was proposed for this species of animals [44].

A common rat model of intervertebral disc degeneration is puncture of the annulus fibrosus with an injury to the gelatinous nucleus. Simultaneous injection (needle 30G, depth 4 mm) of interleukin-1β accelerates the degeneration of the L_V–L_{VI} intervertebral disc in Sprague-Dawley rats [45], which was proven using methods of histology, immunohistochemistry, and magnetic resonance imaging (MRI). The authors consider the proposed model suitable for preclinical testing of drugs designed to treat patients with herniated disc and neuropathic pain. One of the varieties of the described model is the introduction of sodium iodoacetate into the L_{IV}–L_V and L_V–L_{VI} intervertebral discs in Sprague-Dawley rats. As a result, in addition to the decrease in the height of the intervertebral disc and the area of the gelatinous nucleus, there were structural disturbances in the epiphyseal cartilage of the adjacent vertebral bodies and their progressive deformation. This led to the development of a pain syndrome in the animals, which was analyzed by shifting weight from the rear to the front of the foot, standing on tiptoe, and using von Frey tests. The model is accepted as useful for studying the mechanisms of the development of clinical symptoms in structural and functional disorders of the intervertebral disc [46].

In another study, the effectiveness of a combination of rat tail intervertebral disc puncture (21G needle — 0.8 mm diameter, 3 mm depth) and ovariectomy for the development of degenerative disorders in the intervertebral disc was shown histologically and with the help of microMRI [47]. Modifications of the intervertebral disc puncture model are associated with the use of needles of different diameters, which makes it possible to obtain degenerative changes of varying severity [48–50]. J. Qian et al. [49] using MRI and histological analysis established no degenerative changes during 4 weeks after puncturing the intervertebral disc in the tail of rats with a 26G needle (diameter 0.45 mm), an acute damage in case of a 16G needle (1.6 mm), and gradually degenerative changes in 18G (1.2 mm) needle. Accordingly, the diameter of the needle must be chosen depending on the research task. In particular, the authors of a similar study recommended the use of a 21G needle and larger to achieve rapid degeneration of the rat tail disc within 2–4 weeks [48]. A similar conclusion was made by X. Huang et al. [50]. They studied the effect of needle diameter and volume of contrast material (iodine) on the development of intervertebral disc degeneration and established (by radiography, MRI and histology) a significant increase in it using a 21G needle compared to 30G, 3 μl of iodine compared to 2 μl.

Gender differences in the perception of pain due to degeneration of the intervertebral disc were determined on the model of intervertebral disc puncture, namely: in male Sprague–Dawley rats, the pain sensation was stronger than in females, against the background of the absence of a difference in the development of degenerative changes according to histological classification and biomechanical tests [51]. The established differences indicate the need to consider females and males as separate cohorts to determine correlations between damage to the constituent spinal motor segments and the response of the nervous system.

Injury to the locking plate also triggers degeneration of the intervertebral disc due to disruption of its nutrition [48, 52, 53]. Such models are intended to reproduce the degenerative changes of the intervertebral disc, which occur gradually, as in humans. One of the options for such a model in Sprague-Dawley rats is to create a fracture of the body of the tail vertebra by drilling it in the middle and subsequently damaging the locking plate [54]. Also, degeneration of the intervertebral disc was caused by isolation from the feeding vessels of the locking plate on both sides of the intervertebral disc of the tail. This was achieved in Sprague-Dawley rats by drilling the bodies of the tail vertebrae at a distance of 1 mm from the disc and injecting cyanoacrylate into the resulting cavity [53]. A similar effect was obtained after the introduction of 30 μl of absolute ethanol into the closing plate of the tail of rats [52].

To study the functional changes that occur in the notochordal cells of the gelatinous nucleus of the intervertebral disc during adolescence as a result of stress, when their number decreases due to differentiation into chondrocytes, apoptosis, or autophagy, a rat tail compression model is used [55–57]. It is reproduced by compressing the tail with a force of 1.3 MPa temporarily (for several days) [55], or permanently (56 days) with a force of 1.3 MPa using the Ilizarov apparatus [56] or other compression devices [57]. The advantage of the compression model is the constant release of inflammatory mediators (interleukin-1β, interleukin-6, tumor necrosis factor-α) in the intervertebral disc and damage to adjacent nerve fibers, in contrast to the creation of a traumatic injury, which is characterized by only a temporary release of such mediators [58].

Models of spinal instability by resection of arcuate joints in the caudal [59] or lumbar spine [60] of rats are useful for studying the development of degenerative disorders in the intervertebral disc without its traumatic or chemical injury.

At the same time, it can be combined with ovariectomy, resulting in the formation of more pronounced changes [59]. Spinal instability can be achieved by transection of the posterior cervical paravertebral muscles, which, in combination with ovariectomy in Sprague-Dawley rats, causes a decrease in the height of the intervertebral disc and thinning of the end plate [61]. In addition, simulated spinal instability causes impaired walking in rats from the 7th week, provided the arcuate joints are resected at the L_{IV}–L_V level [62].

Models of immobilization of four caudal vertebrae with the help of Kirschner needles passed through them, attached to an external fixation device, were used to obtain degenerative changes in the intervertebral disc of rats [63, 64]. The study showed changes in the biomechanics of the collagen fibrils of the fibrous ring and the matrix of the gelatinous nucleus, inhibition of the expression of type II collagen and aggrecan genes, and an increase in MMP-3, MMP-13. These results should be taken into account in clinical settings when using spinal immobilization. Osteoarthritis of arcuate joints in the lumbar spine of rats is reproduced with the help of intra-articular injection of chemical agents [65–67], mechanical trauma [9, 68] and influence of systemic factors [69].

Intra-articular injection of 2 mg/L of urinary plasminogen activator in 5 μL of physiological solution caused degenerative changes in the arcuate joints as early as on the 7th week [65]. At the same time, intra-articular injection of bacterial collagenase did not damage the joint structure, but caused persistent sensitivity and nociception of the arcuate joints of rats [66]. This model is recommended by the authors as a model of back pain without radiological signs of osteoarthritis of the arcuate joints [66]. Intra-articular injection of Freund's adjuvant (suspension of dried mycobacteria in paraffin oil) also caused the development of osteoarthritis of the arcuate joints [65].

Degeneration of arcuate joints is obtained by compression, for instance, by unilateral placement of a compression spring in the joint at the level of L_{IV}–L_V or L_V–L_{VI} [9]. Post-traumatic osteoarthritis of the arcuate joints developed as a result of percutaneous puncture of the capsule at three levels — L_{III}–L_{VI}, which provided persistent hyperalgesia. The model makes it possible to study the effectiveness of analgesia in rats [68]. Ovariectomy was proposed as an atraumatic model of osteoarthritis of the arcuate joints [69].

To study the mechanisms of degenerative changes in the intervertebral disc, there are several lines of genetically modified mice: with a knockout of the SPARC protein gene [70] and caspase-3 [71], overexpression of β-catenin (for studying osteoarthritis of the arcuate joints) [72].

Models of intervertebral disc or arcuate joint degeneration developed in mice share many features with rat models. In particular, as in rats, intervertebral disc puncture was used in mice: with a 30G needle (diameter 0.3 mm) in the lumbar spine at the L_{IV}–L_V level in CD1 mice [73, 74] and 26G (0.45 mm) in lines C57BL/6J [75], 27G (0.4 mm) [76, 77] or 29G (0.33 mm) [77] in the caudal spine.

Systemic factors, such as obesity, have been used to study the development of degenerative changes in the intervertebral disc of mice. The authors showed that by maintaining male C57BL/6N mice on a high-fat diet for 12–40 weeks, behavioral signs of pain appeared at week 12 and did not disappear until the end of the experiment. Moderate degenerative changes and increased expression of pro-inflammatory cytokines and MMP-1 were found in the intervertebral disc after 40 weeks. The obtained results make it possible to get closer to understanding the relationship between the occurrence of spinal pain, obesity and structural changes in the intervertebral disc [78]. Another systemic approach, used in both mice and rats, is ovariectomy-induced degenerative disorders in arcuate joints [79, 80].

Unilateral osteotomy of the joint in the lumbar spine at the L_{IV}–L_V level in the model of instability was used to study the degeneration of arcuate joints in mice, as well as in rats [81]. Another option is resection in C57BL/6J mice of arcuate joints and supra- and interspinous ligaments in the lumbar spine [82] or spinous processes and these ligaments [83, 84] to model intervertebral disc degeneration.

Thus, to date, many experimental models on small laboratory animals (rabbits, rats, mice) have been developed, validated and used, which are recognized as useful for studying the mechanisms of the development of degenerative diseases of the spine and testing methods of surgical and conservative treatment.

In general, they can be divided into traumatic and chemical damage to the structures of spinal motor segments, the influence of mechanical and systemic factors. The use of such models is simple, easily reproducible and less costly compared to the use of large animal models. Another advantage of small animals (mice) is the possibility of developing models using genetic technologies to obtain disorders of the biosynthesis of certain compounds, which is inherent in a specific disease.

Conclusions

Animal models to study the mechanisms of the development of degenerative disorders in the process of aging or restoration of the structures of the constituent spinal motor segments as a result of testing the latest treatment strategies are an important link of preclinical tests. Historically, laboratory rodents, pigs, goats, dogs, sheep, and primates have been used for this purpose. Each of the animal species has certain advantages and disadvantages for studying the structure, function and biomechanics of the spine.

Modern research in the field of veterinary medicine shows that dogs suffer from spinal diseases with the same frequency as humans. Anatomical, histological and biochemical features of the structures of the spinal column of these animals are quite similar to those of humans, and they undergo the same degenerative changes with age. This makes dogs a good subject for studying spinal diseases and approaches to their treatment. However, high modern bioethical standards and the high cost of research limit the use of large animals in experiments.

Recently, laboratory rodents — rabbits, rats, mice — have been used to simulate degenerative changes in the spine by performing traumatic injuries (surgical disruption of the integrity of ar-

cuate joints, locking plates, annulus fibrosus or gelatinous annulus, nucleotomy, discectomy) and the introduction of chemical agents. These models are characterized by ease of use and reproduction and are economically and ethically justified. A significant number of studies published in recent years confirm the importance and suitability of such models both for elucidating the mechanisms of development of clinical symptoms and degenerative changes in reproducible disorders in the components of the spinal motor segments, and for preclinical tests of the effectiveness of the created treatment strategies. However, the model must be chosen carefully according to the research objectives.

Conflict of interest. The authors declare no conflict of interest.

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MODERN APPROACHES TO MODELING *IN VIVO* DEGENERATIVE SPINE DISEASES

V. O. Radchenko [1], M. A. Skidanov [1], N. O. Ashukina [1], V. Ye. Maltseva [1], A. G. Skidanov [1, 2], O. O. Barkov [1]

[1] Sytenko Institute of Spine and Joint Pathology National Academy of Medical Sciences of Ukraine, Kharkiv
[2] Municipal non-profit enterprise «City Multidisciplinary Hospital No. 18» of the Kharkiv City Council.Ukraine

✉ Volodymyr Radchenko, MD, Prof. in Traumatology and Orthopaedics: volod56@ukr.net
✉ Mykyta Skidanov, Intern doctor in Traumatology and Orthopaedics: skidanov.doc@gmail.com
✉ Nataliya Ashukina, MD, PhD in Biol. Sci.: natalya.ashukina@gmail.com
✉ Valentyna Maltseva, MD, Phd in Biol. Sci.: maltseva.val.evg@gmail.com
✉ Artem Skidanov, DMSci in Traumatology and Orthopaedics: skidanov_artem@ukr.net
✉ Oleksandr Barkov, MD, PhD in Traumatology and Orthopaedics: a.barkov.79@gmail.com