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Experimental Models Used in Neurosurgery Practice and Selection of an Appropriate Model

Nöroşirurji Pratiğinde Kullanılan Deney Modelleri ve Uygun Model Seçimi

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ABSTRACT The role of animal experiments in the progress of medicine and its current stage has a significant effect. Most of the research in the medical and veterinary fields requires the use of experimental animals. It is a possible fact that the next experimental studies will be realized with the contribution of animal experiments. On the other hand, since humans cannot be included in experimental studies due to ethical reasons, the use of animals is mandatory. There are many models in which experimental animals are used. However, the use of experimental animals also brings some disadvantages. Experimental animals cannot be used randomly for scientific or any other purpose. Even if the experimental protocol was carried out properly, it will invalidate the obtained data if the appropriate experimental model is not chosen for the study. If the wrong experimental model is chosen, it will result in both economic and time loss. For these reasons, how and which model will be applied in internal and surgical branches in experimental studies and subject selection constitute an important problem. Choosing a suitable subject for the study increases the applicability of the studies and ensures that positive results can be obtained. In our article, we planned to compile the experimental models applied in the literature with different aspects including their advantages and disadvantages and to provide the practitioner with ease of choice.

Keywords: Animal use; laboratory animal; experimental animal models; proper animal selection

ÖZET Tıbbın ilerlemesinde ve günümüzdeki aşamaya gelmesinde, hayvan deneylerinin rolü önemli ölçüde etkilidir. Tıp ve veteriner alanlarındaki araştırmaların birçoğu deney hayvanı kullanımını gerektirmektedir. Bundan sonra yapılacak olan deneysel çalışmaların da hayvan deneylerinin katkılarıyla gerçekleşmesi olası bir gerçektir. Öte yandan, etik nedenlerden dolayı deneysel çalışmalarda insanlara yer verilememesi, hayvanların kullanımını zorunlu kılmaktadır. Deney hayvanlarının kullanıldığı çok sayıda model bulunmaktadır. Fakat deney hayvanlarının kullanımı, birtakım dezavantajları da beraberinde getirmektedir. Bilimsel olarak ya da herhangi başka bir amaç için deney hayvanları rastgele kullanılamazlar. Deney protokolü uygun yürütülmüş olsa da çalışma için uygun deney modeli seçilmez ise elde edilen verileri geçersiz kılacaktır. Yanlış deney modeli seçildiğinde, hem ekonomik hem de zaman kaybı ile sonuçlanacaktır. Bu nedenle deneysel çalışmalarda, dahili ve cerrahi branşlarda hangi modelin nasıl uygulanacağı ve denek seçimi önemli bir sorun oluşturmaktadır. Çalışmaya uygun denek seçimi, çalışmaların uygulanabilirliğini artırmakta ve olumlu sonuçlar alınabilmesini sağlamaktadır. Yazımızda, literatürde uygulanan deney modellerini avantaj ve dezavantajlarını da içeren farklı yönleriyle derlemeyi ve uygulayıcıya seçim kolaylığı sağlamayı planladık.

Anahtar Kelimeler: Hayvan kullanımı; laboratuvar hayvanı; deneysel hayvan modelleri; uygun hayvan seçimi

Research on scientific and educational experimental models is needed to make cell, tissue, organ, system and inter-system evaluations, to develop disease or new diagnosis and treatment options, and to gain new information about the treatment of diseases or disorders.

When choosing an experimental model, the normal living conditions of the target species and similarities between humans are taken into account.[1] Although being genetically similar to human is important, it does not always guarantee selection as a model. For example, in terms of evolutionary devel-

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opment, chimpanzees are a species closer to humans. They can be infected with human immune deficiency virus (HIV), but the disease picture may not develop. In this case, cats that are less genetically similar to humans can be considered as a more appropriate model because of the presence of Feline Immunodeficiency Virus, a picture similar to the development and findings of acquired immune deficiency syndrome (AIDS) disease caused by the human HIV.[2] At the same time, cost, opportunities and experiences should be reviewed in the selection of the type. If these criteria are considered to be insufficient, support should be obtained from experienced researchers.

Other factors that are effective in determining the experimental model are the plan to be applied and the number of animals to be used, the suitability of the human disease to be studied, the genetic structure, the response of the experimental model to applications, the impact of the environment, housing preferences, the provision of animal comfort and all vital information about reducing fear through basic habit processes.[3-6]

The direct transfer of the information gained from experimental animal models to human remains to the next step and cannot always be guaranteed. At the same time, there is also the use of animals with a disease or damage model that cannot be created under exactly similar conditions to humans.[7]

MODELS ASSOCIATED WITH THE NERVOUS SYSTEM

CHEMICAL PAIN MODEL

Mice are frequently used in antinociceptive tests, where painkillers are tested and the mechanisms related to pain are tried to be elucidated. In these experiments, the mouse's reaction to a thermal, chemical or mechanical ectopic stimulus is measured. Stimulus action is defined as pressure, burning, pain when it rises above the perception of hot or cold. This test is carried out on a hot plate and at a temperature of approximately 50-55 °C. It is based on the principle of measuring the time until the experimental model is placed on the plate and then pulled, jumpedor licked its back foot. The prolongation of the elapsed time is interpreted as an antinociceptive effect. This experiment is often used in the investigation of central pain relievers.[8] For the chemical pain model, the writhing movement caused by intraperitoneal perfusion and active substances such as acetic acid or p-benzoquinone is numerically evaluated and the decrease in the writhing number is interpreted as antinociceptive. This experiment is used to evaluate peripheral pain relievers non-steroid anti-inflammatory drugs-NSAIDs).[9]

NEUROPATHIC PAIN MODEL

The model that forms on the sciatic nerve is one of the easily applicable neuropathic pain models. It is defined as pain that occurs due to a lesion on the nervous system. Unlike nociceptive pain, there is no external stimulation continuously.[10] It usually occurs over a long period of time after nerve damage. Neuropathic pain is characterized by spontaneous pain that produces hypersensitivity to an external stimulus or to a normally harmless stimulus.[11] Rat experimental model is mostly used in neuropathy research.[12]

When rats are fed unlimitedly, they develop Type 2 diabetes due to obesity and it has been determined that allodynia occurs accordingly. In addition, it was found that hyperinsulinemia and allodynia occurred in rats raised with foods containing 40% galactose in their diets.[13]

PERIPHERAL NEUROPATHY MODEL CREATED USING CHEMOTHERAPY DRUGS

Antitumor drugs show significant side effects in most patients. The side effects that occur are especially bone marrow suppression and peripheral neuropathy. These side effects limit chemotherapy application. Experiments with systemic administration of vincristine, cyclophosphamide and doxorubicin show marked allodynia and pain hypersensitivity. Therefore, antitumor drugs are used to create a peripheral neuropathy test model.[14,15]

SPINAL CORD INJURY

Many experimental models have been developed to create trauma to the spinal cord. Current models are weight reduction from height and spinal cord compression with clips. In the method first put forward

by Allen; a known weight is dropped from a certain height onto the spinal cord exposed after laminectomy.[16] Generally, a 10 g weight (50 g/cm) is left to free fall vertically in a pipe from a height of 5 cm to the spinal cord, which is exposed with the help of a device prepared, and a trauma model is created. In the other method, spinal cord damage is created by using an aneurysm clips. The 24-g strength aneurysm clip is kept closed for 1 minute after laminectomy for extradural compression of the spinal cord and a trauma model is created.[17]

MODELS RELATED TO LIVER DISEASES

Liver damage in rats can be caused by factors such as cyclophosphamide, paracetamol, methotrexate and nimesulide. Apart from these applications, hepatotoxicity occurs in every method, although it is formed by different mechanisms. In the experimental model, the effectiveness of the substance used to prevent and treat the damage caused by this toxicity is tried to be measured by biochemical methods, both histologically and by looking at the levels of enzymes such as alanine aminotransferase.[18]

MODELS RELATED TO LUNG DISEASES

ASTHMA MODEL

Although asthma is a diffuse occupational disease, its pathophysiology remains uncertain.[19] As research on asthma became widespread, it was understood that it was a more complex disease, triggered by many cellular factors. In order to better analyze the development of the disease, the disease and its clinical symptoms must first be defined. For ethical reasons, it is not possible to use humans as an experimental model to understand the mechanism at the cellular or molecular level.[20] For this reason, animal models are particularly needed. A system is developed to determine the targets of drug therapies for the purpose of examining or experimental models are characteristic. The most popular animal models are rodents (inbred mice and rats), guinea pigs, rabbits. The use of these models is more readily available than other models (hamsters, dogs, sheep, horses and monkeys were also used to develop an asthma model) and is preferred because they are more cost-effective than others.[21]

Each experimental model has its advantages and disadvantages. When the studies are examined, it has been observed that guinea pigs, a group close to rodents, have similar interactions between human and guinea pig airways when exposed to allergens, asthma-related drugs and dermatological effects, especially due to their sensitivity to methacholine and histamine.[22] Allergic asthma models are created by first exposing the experimental animal to a foreign protein, the most commonly used ovaalbumin aerosol.[23,24]

LUNG CANCER MODEL

The lung cancer model is the most fatal cancer type in the world.[25] In order to understand cancer etiology and to develop new treatments, mouse models showing cancer clinical features are needed. These models are critical in mimicking both tumor development and histological features in a lung cancer model.

Xenograft Model

In this experimental model, cancer cells are transplanted into a region of the organ of origin. This organ-specific area is an environment in optimal conditions for the growth and development of the cancer cell. This costly and unconventional model is used to evaluate the effects of organ site-specific cytotoxic agents in vivo in conditions such as lung cancer. Currently, renal cell carcinoma, pancreatic carcinoma, brain tumors, prostate, colon and lung cancers with nude mice are potential orthotopic model uses.[26] In the lung tumor cell, the suspended cancer cells are inoculated directly into the right bronchial stem of the anesthetized animal's right lung.[27]

Tumor formation can be interpreted by sacrificing the animal. Histologically, the tumor is evaluated. Xenograft models are often used to investigate the response of cancer cells to treatment. Tumor development varies depending on the type, size, density and use of growth factors, with the optimum number of cells to be transferred between 106 and 107.[28] In this model, the source of the transplanted tumor can be the cancer cell line, or it is possible by orthotopically transplanting the tumor tissue from human lung cancer. Cell lines A549, H1975, HCC4006 and HCC827 are most commonly used to induce adenocarci-

noma.[29-32] Cell lines NCI-H1299 for carcinomas, NCI-H460 for large cell carcinomas, and NCI-H226 for squamous cell carcinomas are the most commonly used sequences.[33-37] When NCI-H460 is transferred to athymic nude mice, it has an advantage over other cell lines in that small amounts of cells are sufficient, proliferate in a shorter time, and 0% rejection.[30,38]

Syngeneic Model

In this model, orthotopic murine models are performed by injection of immunocompatible tumor cells into immunocompatible mice. This model is very difficult and limited to create. The advantage of this model is that the injected cells are immunologically compatible with the murine model, which reflects the disease better than other models. The only syngeneic model created to date is Lewis Lung Carcinoma (LAC). The LAC cell line is highly tumorigenic and is used especially in metastasis studies.[39] For the first time, the C57BL/6 strain was found spontaneously in the lung of a mouse in 1951. It can be administered to mice via two separate injections.

MODELS RELATED TO CARDIOVASCULAR DISEASES

Hypertension is one of the important circulatory diseases that occur with different types depending on many reasons. Small rodents (rat, mouse, rabbit) and large animal models (dog, pig, sheep) are used as experimental models in cardiovascular diseases. Rats are frequently preferred in cardiovascular (KDV) diseases thanks to many advantages they provide such as cheaper housing and care than large animals, easy and repeatable application, and the use of more subjects in terms of statistical evaluation. In addition, in rat models, it is more convenient to measure cardiac function tests and open heart surgery compared to mice. Since the heart mass ratio of the rat experimental model has a larger volume compared to the mouse model, it provides convenience in postmortem, molecular and histological studies. While rat models are used to discover potential new pharmacological or molecular agents for the treatment of heart disease, mouse models are used to discover molecular or pharmacological treatment pathways with important gene or protein targeting. Mouse experimental models are used for gene sequencing, protein studies, and studies at the drug or molecular level.[40,41] Rats are loaded with high doses of salt over a long period of time to investigate this serious disease that damages many systems.[42] Rats called spontaneous hypertensive rats are animals that spontaneously develop hypertension without any application exogenously.[43]

Hypertension in rats can be induced using the deoxycorticosterone acetate and salt (DOCA-salt) hypertension model. The DOCA-salt hypertension model is a convenient method that can mimic neurohumoral and metabolic changes among experimental hypertension models. The formation process of the DOCA-salt hypertension model in experimental animals constitutes a chronic malignant pathology and in this process leads to dysfunction, especially in the vessels.[44] Hypertension induced by the administration of mineralocorticoids is an endocrine-derived method developed more than 60 years ago and is still the most widely used.[45-47] First demonstrated hypertension in rats treated with 11-DOCA-salt. Subcutaneous injection of DOCA at high doses of approximately 300 to 1,000 mg/kg/day is sufficient to induce hypertension in rats. It has been reported that DOCA causes more rapidly developing and more severe hypertension in male rats compared to female rats.[48] In the hypertension model induced by glucocorticoids, hypertension is induced by administration of excessive amounts of glucocorticoids to healthy animals.[49] Although glucocorticoids induce hypertension through renin angiotensin aldosterone system (RAAS) activity in rats and mice, their efficacy it is lower than the DOCA-salt.[49,50]

An important parameter in heart diseases is blood fluidity (hemoreology). Negative changes in blood fluidity (increase in viscosity) or related parameters such as erythrocyte deformability, erythrocyte aggregation, plasma viscosity and hematocrit are associated with cardiovascular disease.[51] In studies on blood fluidity, mammals are used to model the properties of human blood. To study the behavior of non-mammalian vertebrates (birds, reptiles, amphibians and fishes contain red blood cells nuclei. Mamalia class mamalia and its subclasses such as

placentals, marsupials and monotremates).[52] Rats and guinea pigs are preferred in these studies because of their higher blood volume than mice.

MODELS RELATED TO DIABETES AND METABOLIC SYNDROME

Metabolic syndrome is a metabolic disorder characterized by genetic and environmental factors, disease risks associated with rapid population growth in the world, insulin resistance, hypertension, obesity and dyslipidemia. Components of the metabolic syndrome adversely affect human health as well as the health of animals, primarily horses, dogs and cats.[53] First Reaven in 1988; This clinical entity, which manifests with hyperinsulinemia, atherogenic dyslipidemia, high blood pressure, high blood glucose levels and / or resistance to insulin-induced glucose intake, has been first defined as "syndrome X" by Reaven in 1988.[54,55] In the following years, names such as "killing quartet" due to increasing cardiovascular risk, and "fatal orchestra" with the presence of high erythrocytosis and uric acid were given.[56,57]

Research is being conducted to elucidate the components of metabolic syndrome that threaten human and animal health so much, and experimental animal models are frequently used. There are many models used in metabolic syndrome experimental studies. Rodents, especially mice, are preferred because their gene maps are well known, inexpensive and easily available, and there are many mutant lineages available.[58]

GENETIC MODELS

Genetic models contribute to the evaluation of molecular mechanisms associated with the development of obesity and metabolic syndrome in experimental models. In addition, the metabolic syndrome seen in humans does not have monogenic properties as in rodents. For example, some experimental models have mutations in the leptin gene and/or its receptors. In humans, only four mutations have been reported to date, and there is a very rare recessive genetic disorder.[59]

ob/ob (C57BL/6J-ob/ob) MOUSE

It is the first genetic model used in diabetes research. They carry an autosomal recessive mutation in the leptin gene on chromosome 6. As a result of the mutation in the leptin gene, the picture of obesity, hyperinsulinemia and hyperglycemia begins to develop after 4 weeks, and glucose tolerance occurs towards the end of the 12th week. In the following weeks, the development of left ventricular hypertrophy, cardiac fibrosis, inflammation and fatty liver are observed as a result of increased cardiac function. At the same time, an increase in body weight is observed in these animals.[59,60]

db/db (C57BL/KsJ-db/db) MOUSE

There is a mutation in the leptin receptor on chromosome 4 in db/db mice. The receptor cannot fulfill its function due to the mutation and there is no response to leptin. Increase in blood glucose concentrations is observed. Insulin resistance can be stuck before hyperglycemia. At the 13th week, increased plasma triglyceride and total cholesterol values are observed. Vascular endothelial dysfunction occurs at 12 weeks.[59,61]

ZUCKER FATTY WITH DIABETES RAT

They carry mutations in the leptin receptor gene. Fasting glucose levels are very high, but not at diabetic levels. Insulin levels are 10-20 times higher than normal. Hypertriglyceridemia, diastolic and systolic dysfunction are seen. Inflammation markers such as cholesterol amount, tumor necrosis factor-alpha and interleukin-1beta increased in serum.[59,62]

METABOLIC SYNDROME INDUCED BY HIGH FAT DIET

In general, obesity is observed in experimental models fed diets containing more than 30% of total energy. Animal models induced by a high-fat diet are the most effective method used to induce insulin resistance, dyslipidemia and obesity.[63,64] There are different high fat diet compositions used to induce metabolic syndrome in experimental animals. In these different types of protocols, 20%-60% of the energy is obtained from animal or vegetable oils.

FRUCTOSE-INDUCED METABOLIC SYNDROME

Fructose causes dysregulation of some signal factors, increasing the likelihood of metabolic syndrome. It is used as a metabolic syndrome model because of its high fructose consumption, metabolic hormone

changes, inflammation and its effect on plasma uric acid level. Sprague-Dawley and Wistar rats can develop metabolic syndrome within 2 weeks.[65]

HIGH CARBOHYDRATE-HIGH FAT-INDUCED METABOLIC SYNDROME

It is suggested that this model is the best model for human metabolic syndrome because of all the complications associated with human metabolic syndrome occurring in rodents fed a high- carbohydrate-high-fat diet, and the similarity of this combination to human diets (cafeteria diet).[59]

In a study in rats, the mechanism of lipid increase in white adipose tissue under the pumice of a low protein-high carbohydrate diet was investigated and concluded that this increase in adipose tissue was due to an increase in glycerol phosphorylation and fatty acid uptake from circulating lipoproteins as well as a decrease in norepinephrine-induced lipolysis.[66]

OTHER MODELS

One of the model animals used in diabetes and obesity animal models is the Otsuka Long-Evans Tokushima Fatty model. In this model, high blood glucose levels are observed at 18 weeks, while glucose tolerance usually begins at 24 weeks. As from the 8th week, cholesterol levels begin to increase, and cardiac hypertrophy and diastolic-systolic blood pressure dysfunction are also observed.

Goto-Kakizaki rats are non-obese and spontaneous diabetic models. This model, which has glucose intolerance, moderate hirperinsulinemia and insulin resistance for a long time, has an experimental advantage because it is stable. In this model, the cell cannot recognize glucose and shows an unresponsiveness to glucose. Cardiac hypertrophy, increased plasma and liver lipid concentrations are seen.[59,67]

INSUFFICIENT OR MISSING MODEL SELECTION

Choosing the correct mouse model is an important challenge in experimental intestinal inflammation studies. Quite detailed evaluations, available from different models, have been published in previous studies.[68-70] However, many authors avoid giving suggestions on the best method to use. Indeed, if an opinion is to be reached, it remains very limited. There are multiple models of chemically induced acute colitis. These are widely preferred as they are easy to use, fast and economical. However, these models may not be the best experimental model to be used in the inflammatory bowel disease (IBD) study. Because chemical damage causes an acute self-limiting inflammation in the intestinal epithelium rather than chronic inflammation. In the comparative analysis of colonic gene expression, 2,4,6-trinitrobenzenesulfonic acid (TNBS), dextran sulfate sodium (DSS) and human IBD T-cell transfer models result in the gene cell expression motif in the T-cell transfer model best predicting variable gene expression in IBD. It has been seen to be a reflecting model.[71] If chemically-induced models are to be used, they should only be used to study the physiology of intestinal wound healing or epithelial regeneration. In addition, there is no single experimental colitis model that is similar in all aspects to human IBD. When choosing which model to use, the research question and IBD subtype should be combined to get the best result.

INSUFFICIENT USE OF RESULTS PARAMETERS

It is a common problem to decide what the most important disease parameter / primary endpoint is in basic or translational studies using animal models, such as in human studies. Intestinal histological (histopathological) semi-quantitative evaluation is considered the gold standard in animal models of intestinal inflammation. However, histology-based scoring systems have not been used properly in the literature. Most of these scoring systems have different subscores in the histological abnormalities seen in experimental models, such as crypt cell loss or immune cell infiltration. There are different sub-parameters for different models, eg for epithelial destruction in the DSS model, or for epithelial hyperplasia in the T-cell transfer model.[72] For this reason, the most important scoring system should be preferred for the model.

Pathological slides should be blunted extensively without any reference to a test animal or experimental group. Since histolopathological scores

allow for an ordinary reading (eg 0 1, 2, ...) the median value is the most appropriate measure used for the central tendency within groups. This prevents the calculation of the required number of animals per group because the average gradient is used to calculate the group size.[73]

DISEASE SUSCEPTIBILITY MAY DIFFER BETWEEN GENDERS

In many autoimmune diseases, there is a marked difference in sensitivity between the sexes, with females being affected more often than males.[74] Gender-related effects have been described in experimental colitis models. In DDS colitis, susceptibility to males is higher, 2,4,6-TNBS colitis has also been shown to be more effective in female mice.[75] Most experiments are done with either male or female mice. However, in possible experiments using both genders, differences among subjects can be observed when a comparison between experiments is made.[71,76]

CONCLUSION

Experimental animals constitute the basically the first step of research. There may be other good reasons to prefer one genre over another. Researchers should select the animal species most likely to produce valid results, with a predisposition to an intended disease process, a propensity to engage in a targeted behavior, the appropriate size for the experimental techniques to be used.

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During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hasan Emre Aydın;* ***Design:*** *Hasan Emre Aydın;* ***Control/Supervision:*** *Hasan Emre Aydın;* ***Data Collection and/or Processing:*** *Nuray Varol Kayapunar, Hasan Emre Aydın;* ***Analysis and/or Interpretation:*** *Hasan Emre Aydın;* ***Literature Review:*** *Nuray Varol Kayapunar;* ***Writing the Article:*** *Nuray Varol Kayapunar, Hasan Emre Aydın;* ***Critical Review:*** *Hasan Emre Aydın.*

REFERENCES

1. Henry J, Baker J, Russell L. Research in laboratory animal and comparative medicine. In: James G, Fox Lynn C, Anderson Franklin M, Loew Fred W, eds. Laboratory Animal Medicine. 2nd ed. Amsterdam, Netherlands: Academic Press; 2002. p.1228-37.
2. Hau J. Handbook of Labora¬tory Animal Science Vol II Animal Models. Hau j, Van Hoosier L. ed. Induced (Experimental) Disease Models. 2nd ed. Boca Raton, US: CRC Press; 2003. p.1-9.[Crossref] [PMC]
3. Barbee RW, Turner PV. Incorporating laboratory animal science into responsible biomedical research. ILAR J. 2019;31;60(1):9-16. [Crossref] [PubMed]
4. de Aguilar-Nascimento JE. Fundamental steps in experimental design for animal studies. Acta Cir Bras. 2005;20(1):2-8.[Crossref] [PubMed]
5. Lipman NS, Perkins SE. Factors that may influence animal research. In: Fox J, Anderson L, Loew F, Quimby F, eds. Laboratory Animal Medicine. 2nd ed. Amsterdam, Netherlands: Academic Press; 2002; p.1143-65.[Crossref]
6. Wood MW, Hart LA. Selecting appropriate animal models and strains: making the best use of research, information and outreach. AATEX. 2008;14 Special Issue:303-6.[Link]
7. van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, O'Collins V, et al. Can animal models of disease reliably inform human studies? PLoS Med. 2010;30;7(3):e1000245. [Crossref] [PubMed] [PMC]
8. Eddy NB, Leimbach D. Synthetic analgesics. II. Dithienylbutenyl- and dithienylbutylamines. J Pharmacol Exp Ther. 1953;107(3):385-93. [PubMed]
9. Koster R, Anderson M, De Beer EJ. Acetic acid for analgesic screening. Federation Proceedings. 1959;18(1):412-7.[Link]
10. Raj PP. Ağrı taksonomisi. Erdine S, editör. Ağrı. 1. Baskı. İstanbul: Alemdar Ofset; 2000. p.12-20.
11. Jensen TS, Gottrup H, Sindrup SH, Bach FW. The clinical picture of neuropathic pain. Eur J Pharmacol. 2001;19;429(1-3):1-11.[Crossref] [PubMed]
12. Wang LX, Wang ZJ. Animal and cellular models of chronic pain. Adv Drug Deliv Rev. 2003;28;55(8):949-65. [Crossref] [PubMed]
13. Wuarin-Bierman L, Zahnd GR, Kaufmann F, Burcklen L, Adler J. Hyperalgesia in spontaneous and experimental animal models of diabetic neuropathy. Diabetologia. 1987;30(8): 653-8.[PubMed]
14. Cavaletti G, Tredici G, Braga M, Tazzari S. Experimental peripheral neuropathy induced in adult rats by repeated intraperitoneal administration of taxol. Exp Neurol. 1995;133(1):64-72.[Crossref] [PubMed]
15. Authier N, Fialip J, Eschalier A, Coudoré F. Assessment of allodynia and hyperalgesia after cisplatin administration to rats. Neurosci Lett. 2000;15;291(2):73-6.[Crossref] [PubMed]
16. Vural A, Özatik rslan A, Uzunlar K. Deneysel spinal kord travmalarında dopamin ile kombine nimodipin ve nalorfinin etkileri. Ankara Patoloji Bülteni. 1994;11(2):21-5.[Link]

17. Döşoğlu M, Kırış T, İzgi N, Ünal ÖF. Omurilik travmalarında ikincil hasar mekanizmaları. Ulus Travma Acil Cerrahi Derg. 1998;4(3):147-57.[Link]
18. Montilla MP, Cabo J, Navarro MC, Risco S, Jimenez J, Aneiros J, et al. The protective and curative action of Withania frutescens leaf extract against CCl4-induced hepatotoxicity. Phytotherapy Research. 1990;4(6):212-5. [Crossref]
19. Chan-Yeung M. A clinician's approach to determine the diagnosis, prognosis, and therapy of occupational asthma. Med Clin North Am. 1990;74(3):811-22.[Crossref] [PubMed]
20. Bousquet J, Jeffery PK, Busse WW, Johnson M, Vignola AM. Asthma. From bronchoconstriction to airways inflammation and remodeling. Am J Respir Crit Care Med. 2000; 161(5):1720-45.[Crossref] [PubMed]
21. Dietrich WF, Miller J, Steen R, Merchant MA, Damron-Boles D, Husain Z, et al. A comprehensive genetic map of the mouse genome. Nature. 1996;14;380(6570):149-52. Erratum in: Nature. 1996;9;381(6578):172.[Crossref] [PubMed]
22. Elias JA, Lee CG, Zheng T, Ma B, Homer RJ, Zhu Z, et al. New insights into the pathogenesis of asthma. J Clin Invest. 2003;111(3):291-7.[Crossref] [PubMed] [PMC]
23. Boskabady MH, Rahbardar MG, Jafari Z. The effect of safranal on histamine (H(1)) receptors of guinea pig tracheal chains. Fitoterapia. 2011;82(2):162-7.[Crossref] [PubMed]
24. Zosky GR, von Garnier C, Stumbles PA, Holt PG, Sly PD, Turner DJ, et al. The pattern of methacholine responsiveness in mice is dependent on antigen challenge dose. Respir Res. 2004;23;5(1):15.[Crossref] [PubMed] [PMC]
25. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008;83(5):584-94. [Crossref]
26. Howard RB, Chu H, Zeligman BE, Marcell T, Bunn PA, McLemore TL, et al. Irradiated nude rat model for orthotopic human lung cancers. Cancer Res. 1991;15;51(12):3274-80. [PubMed]
27. Hastings RH, Burton DW, Quintana RA, Biederman E, Gujral A, Deftos LJ, et al. Parathyroid hormone-related protein regulates the growth of orthotopic human lung tumors in athymic mice. Cancer. 2001;15;92(6):1402-10. [Crossref] [PubMed]
28. Kellar A, Egan C, Morris D. Preclinical murine models for lung cancer: clinical trial applications. Biomed Res Int. 2015;2015:621324. [Crossref] [PubMed] [PMC]
29. Memon AA, Jakobsen S, Dagnaes-Hansen F, Sorensen BS, Keiding S, Nexo E, et al. Positron emission tomography (PET) imaging with [11C]-labeled erlotinib: a micro-PET study on mice with lung tumor xenografts. Cancer Res. 2009;1;69(3):873-8.[Crossref] [PubMed]
30. Steiner P, Joynes C, Bassi R, Wang S, Tonra JR, Hadari YR, et al. Tumor growth inhibition with cetuximab and chemotherapy in non-small cell lung cancer xenografts expressing wild-type and mutated epidermal growth factor receptor. Clin Cancer Res. 2007;1;13(5):1540-51.[Crossref] [PubMed]
31. Sakuma Y, Matsukuma S, Nakamura Y, Yoshihara M, Koizume S, Sekiguchi H, et al. Enhanced autophagy is required for survival in EGFR-independent EGFR-mutant lung adenocarcinoma cells. Lab Invest. 2013;93(10): 1137-46. [Crossref] [PubMed]
32. Akhtar S, Meeran SM, Katiyar N, Katiyar SK. Grape seed proanthocyanidins inhibit the growth of human non-small cell lung cancer xenografts by targeting insulin-like growth factor binding protein-3, tumor cell proliferation, and angiogenic factors. Clin Cancer Res. 2009;1;15(3):821-31. Erratum in: Clin Cancer Res. 2018;1;24(23):6101.[Crossref] [PubMed]
33. Chen MF, Chen WC, Wu CT, Lin PY, Shau H, Liao SK, et al. p53 status is a major determinant of effects of decreasing peroxiredoxin I expression on tumor growth and response of lung cancer cells to treatment. Int J Radiat Oncol Biol Phys. 2006;1;66(5):1461-72. [Crossref] [PubMed]
34. Wang H, Li M, Rinehart JJ, Zhang R. Pretreatment with dexamethasone increases antitumor activity of carboplatin and gemcitabine in mice bearing human cancer xenografts: in vivo activity, pharmacokinetics, and clinical implications for cancer chemotherapy. Clin Cancer Res. 2004;1;10(5):1633-44.[Crossref] [PubMed]
35. McLemore TL, Liu MC, Blacker PC, Gregg M, Alley MC, Abbott BJ, et al. Novel intrapulmonary model for orthotopic propagation of human lung cancers in athymic nude mice. Cancer Res. 1987;1;47(19):5132-40. [PubMed]
36. Carter CA, Chen C, Brink C, Vincent P, Maxuitenko YY, Gilbert KS, et al. Sorafenib is efficacious and tolerated in combination with cytotoxic or cytostatic agents in preclinical models of human non-small cell lung carcinoma. Cancer Chemother Pharmacol. 2007;59(2):183-95.[Crossref] [PubMed]
37. Feng Z, Zhao G, Yu L, Gough D, Howell SB. Preclinical efficacy studies of a novel nanoparticle-based formulation of paclitaxel that outperforms Abraxane. Cancer Chemother Pharmacol. 2010;65(5):923-30. [Crossref] [PubMed] [PMC]
38. Yamori T, Sato S, Chikazawa H, Kadota T. Anti-tumor efficacy of paclitaxel against human lung cancer xenografts. Jpn J Cancer Res. 1997;88(12):1205-10. [Crossref] [PubMed] [PMC]
39. Sakai Y, Sasahira T, Ohmori H, Yoshida K, Kuniyasu H. Conjugated linoleic acid reduced metastasized LL2 tumors in mouse peritoneum. Virchows Arch. 2006;449(3):341-7.[Crossref] [PubMed]
40. Akbay E, Onur MA, Gürpınar ÖA. [Myocardial infarction models]. Turkiye Klinikleri J Cardiovasc Surg-Special Topics. 2013;5(3):49-57. [Link]
41. Karasu-Minareci E, Öğütman Ç. [Experimental animal models for cardiovascular diseases]. Turkiye Klinikleri J Cardiovasc Sci. 2011;23(1):65-74.[Link]
42. Bopda OS, Longo F, Bella TN, Edzah PM, Taïwe GS, Bilanda DC, et al. Antihypertensive activities of the aqueous extract of Kalanchoe pinnata (Crassulaceae) in high salt-loaded rats. J Ethnopharmacol. 2014;28;153(2):400-7.[Crossref] [PubMed]
43. Qui-ones M,Guerrero L, Suarez M, Pons Z, Aleixandre A, Arola L, et al. Low-molecular procyanidin rich grape seed extract exerts antihypertensive effect in males spontaneously hypertensive rats. Food Research International. 2013;51(2):587-95.[Crossref]
44. Sun ZJ, Zhang ZE. Historic perspectives and recent advances in major animal models of hypertension. Acta Pharmacol Sin. 2005;26(3):295-301.[Crossref] [PubMed]
45. Selye H. Production of nephrosclerosis by overdosage with desoxycorticosterone acetate. Can Med Assoc J. 1942;47(6):515-9. [PubMed] [PMC]
46. Terris JM, Berecek KH, Cohen EL, Stanley JC, Whitehouse WM Jr, Bohr DF, et al. Deoxycorticosterone hypertension in the pig. Clin Sci Mol Med Suppl. 1976;3:303s-5s. [Crossref] [PubMed]
47. Bois P, Selye H. The hormonal production of nephrosclerosis and periarteritis nodosa in the primate. Br Med J. 1957;26;1(5012):183-6.[Crossref] [PubMed] [PMC]
48. Crofton JT, Share L. Gonadal hormones modulate deoxycorticosterone-salt hypertension in male and female rats. Hypertension. 1997;29(1 Pt 2):494-9.[Crossref] [PubMed]
49. Dahl LK, Heine M, Tassinari L. Effects of chronic excess salt ingestion. Further demonstration that genetic factors influence the development of hypertension: evidence from experimental hypertension due to cortisone and to adrenal regeneration. J Exp Med. 1965;1;122(3):533-45.[Crossref] [PubMed] [PMC]
50. Knowlton AI, Loeb EN, Stoerk HC, Whıte JP, Heffernan JF. Induction of arterial hypertension in normal and adrenalectomized rats given cortisone acetate. J Exp Med. 1952; 96(3):187-205. [Crossref] [PubMed] [PMC]
51. Ergül Erkeç Ö. Tıbbi çalışmalarda hayvan modelleri. Int J Hum Sci Uluslararası İnsan Bilim Derg. 2014;50-63.[Crossref]

52. Baskurt OK, Marshall-Gradisnik S, Pyne M, Simmonds M, Brenu E, Christy R, et al. Assessment of the hemorheological profile of koala and echidna. Zoology (Jena). 2010;113(2):110-7.[Crossref] [PubMed] [PMC]
53. Bailey SR, Habershon-Butcher JL, Ransom KJ, Elliott J, Menzies-Gow NJ. Hypertension and insulin resistance in a mixed-breed population of ponies predisposed to laminitis. Am J Vet Res. 2008;69(1):122-9. [Crossref] [PubMed]
54. Reaven GM. Role of insulin resistance in human disease. Diabetes. 1988;37(12):1595-1607.[Crossref] [PubMed]
55. Emanuela F, Grazia M, Marco de R, Maria Paola L, Giorgio F, Marco B, et al. Inflammation as a link between obesity and metabolic syndrome. J Nutr Metab. 2012;2012:476380. [Crossref] [PubMed] [PMC]
56. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med. 1989;149(7):1514-20.[Crossref] [PubMed]
57. Kim SH, Reaven GM. The metabolic syndrome: one step forward, two steps back. Diab Vasc Dis Res. 2004;1(2):68-75.[Crossref] [PubMed]
58. Caltabilota TJ, Earl LR, Thompson DL Jr, Clavier SE, Mitcham PB. Hyperleptinemia in mares and geldings: assessment of insulin sensitivity from glucose responses to insulin injection. J Anim Sci. 2010;88(9):2940-9.[Crossref] [PubMed]
59. Panchal SK, Brown L. Rodent models for metabolic syndrome research. J Biomed Biotechnol. 2011;2011:351982. [Crossref] [PubMed] [PMC]
60. Polotsky VY. Mouse model of the metabolic syndrome: the quest continues. J Appl Physiol (1985). 2007;102(6):2088-9. [Crossref] [PubMed]
61. Sharma K, McCue P, Dunn SR. Diabetic kidney disease in the db/db mouse. Am J Physiol Renal Physiol. 2003;284(6):F1138-44. [Crossref] [PubMed]
62. Shafrir E, Ziv E. A useful list of spontaneously arising animal models of obesity and diabetes. Am J Physiol Endocrinol Metab. 2009;296(6): E1450-2.[Crossref] [PubMed]
63. Silva APS, Guimarâes DED, Mizurini DM, Maia IC, Ortiz-Costa S, Sardinha FL, et al. Dietary fatty acids early in life affect lipid metabolism and adiposity in young rats. Lipids. 2006;41(6):535-41. [Crossref] [PubMed]
64. Akagiri S, Naito Y, Yoshikawa T. Diyet and metabolic syndrome. J Biol Macromol. 2009;9(2):39-48.[Link]
65. Basciano H, Federico L, Adeli K. Fructose, insulin resistance, and metabolic dyslipidemia. Nutr Metab (Lond). 2005;21;2(1):5.[Crossref] [PubMed] [PMC]
66. Santos MP, França SA, Santos JT, Buzelle SL, Bertolini GL, Garófalo MA, et al. A low-protein, high-carbohydrate diet increases fatty acid uptake and reduces norepinephrine-induced lipolysis in rat retroperitoneal white adipose tissue. Lipids. 2012;47(3):279-89.[Crossref] [PubMed]
67. Desrois M, Sidell RJ, Gauguier D, King LM, Radda GK, Clarke K, et al. Initial steps of insulin signaling and glucose transport are defective in the type 2 diabetic rat heart. Cardiovasc Res. 2004;1;61(2):288-96.[Crossref] [PubMed]
68. Mizoguchi A, Mizoguchi E. Animal models of IBD: linkage to human disease. Curr Opin Pharmacol. 2010;10(5):578-87. [Crossref] [PubMed] [PMC]
69. DeVoss J, Diehl L. Murine models of inflammatory bowel disease (IBD): challenges of modeling human disease. Toxicol Pathol. 2014;42(1):99-110.[Crossref] [PubMed]
70. Jones-Hall YL, Grisham MB. Immunopathological characterization of selected mouse models of inflammatory bowel disease: Comparison to human disease. Pathophysiology. 2014;21(4):267-88.[Crossref] [PubMed]
71. te Velde AA, de Kort F, Sterrenburg E, Pronk I, ten Kate FJ, Hommes DW, et al. Comparative analysis of colonic gene expression of three experimental colitis models mimicking inflammatory bowel disease. Inflamm Bowel Dis. 2007;13(3):325-30. [Crossref] [PubMed]
72. Erben U, Loddenkemper C, Doerfel K, Spieckermann S, Haller D, Heimesaat MM, et al. A guide to histomorphological evaluation of intestinal inflammation in mouse models. Int J Clin Exp Pathol. 2014;15;7(8):4557-76. [PubMed] [PMC]
73. Gibson-Corley KN, Olivier AK, Meyerholz DK. Principles for valid histopathologic scoring in research. Vet Pathol. 2013;50(6):1007-15. [Crossref] [PubMed] [PMC]
74. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol. 2014;35(3):347-69.[Crossref] [PubMed]
75. Bouma G, Kaushiva A, Strober W. Experimental murine colitis is regulated by two genetic loci, including one on chromosome 11 that regulates IL-12 responses. Gastroenterology. 2002;123(2):554-65. [Crossref] [PubMed]
76. Alex P, Zachos NC, Nguyen T, Gonzales L, Chen TE, Conklin LS, et al. Distinct cytokine patterns identified from multiplex profiles of murine DSS and TNBS-induced colitis. Inflamm Bowel Dis. 2009;15(3):341-52.[Crossref] [PubMed] [PMC]