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Research Progress of Animal Models in Metabolic Syndrome

Aixuan Du

Xi'an GaoXin No.1 High school, Xi'an, Shaanxi, 710061, China

2222003789@qq.com

Abstract. Animal models are frequently employed in illness research, mostly for investigations on experimental pathology, physiology, and therapeutics. This paper introduces that animal models play an important role in the study of metabolic syndrome based on existing literature and data. The result shows that metabolic syndrome encompasses a range of metabolic disorders caused by factors such as poor diet and lack of exercise. Clinical manifestations include obesity, hyperglycemia and hypertension. The advantages of using animal models include the ability to control environmental factors and facilitate intervention research. However, there are also disadvantages, such as physiological differences between animals and humans. Commonly used animal models include mouse models, such as obese mice induced by high fat diet, which can simulate the characteristics of human metabolic syndrome. In the future, the development of new, more human-like models may allow for better replication of the disease and more accurate studies.

Keywords: Animal Models, Human Diseases, Clinical Manifestations, Metabolism, Pathology.

1. Introduction

It has long been a habit to utilise non-human animals in studies to increase public knowledge of human biology and health. For example, using animal models enables researchers to carefully modify environmental elements to learn more about how they affect behaviour, development, and health. Access to tissue-specific metabolism, which is frequently impossible to study in humans, has been made available by animal models. This makes them instrumental in understanding the occurrence and progression of human diseases, as well as in the development of prevention and control measures. Animal models have made significant contributions to biomedical science by enhancing people's understanding of pathological and biological processes [1]. Metabolic syndrome is a variety of metabolic disorders caused by poor diet, lack of exercise, and other factors. John Speakman, Catherine Hambly, and other scholars have utilized mouse models to investigate the relationship between obesity and metabolism. Their findings suggest that while obesity can cause a variety of diseases, the adverse metabolic outcomes associated with metabolic syndrome are only associated with abdominal fat, not overall body fat [2]. Researchers such as Carlos Zaragoze, Carmen Gomez-Guerreo, and Jose Luis Martin-Ventura have used mouse models to study multiple causes of atherosclerosis, observing that the likelihood of atherosclerotic lesions is worsened by risk factors such as hypertension or diabetes [3]. The study plays an important role in the treatment and research of diseases in the medical field. Animal models help to deeply understand the diseases related to human metabolism and the pathogenesis of

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related diseases and provide a strong basis for the development of new treatment methods and drug research.

2. Advantages and limitations about animal model

There are some advantages and limitations regarding animal models. The analysis is listed as follows.

2.1. Advantages

Animal models offer researchers a high degree of control over experimental variables. For instance, researchers can regulate animals' diets, environments, and drug exposure to better study specific physiological processes or diseases. Scientists usually use drugs or control the environment to make animals show the same pathology as humans.

Reproducibility: Animal models can be reused, allowing researchers to repeat experiments to validate and confirm the reliability and stability of the research results. This reproducibility is essential for the development and testing of drugs, vaccines, and surgical techniques applicable to humans.

One example is Caenorhabditis elegans, which has a short life cycle — spanning only 2-3 weeks from the L4 larval stage to adult death — making it ideal for measuring the effects of anti-ageing drugs(Figure 1). C. elegans has a completely sequenced and annotated genome, and worms are very receptive to genetic alterations using cutting-edge genome-editing techniques like CRISPR as well as conventional forward/reverse genetic screening. The brief lifespan of this organism is also helpful for researching biological issues like longevity. In contrast, high-throughput analytical constraints and expense frequently limit investigations using mouse models.

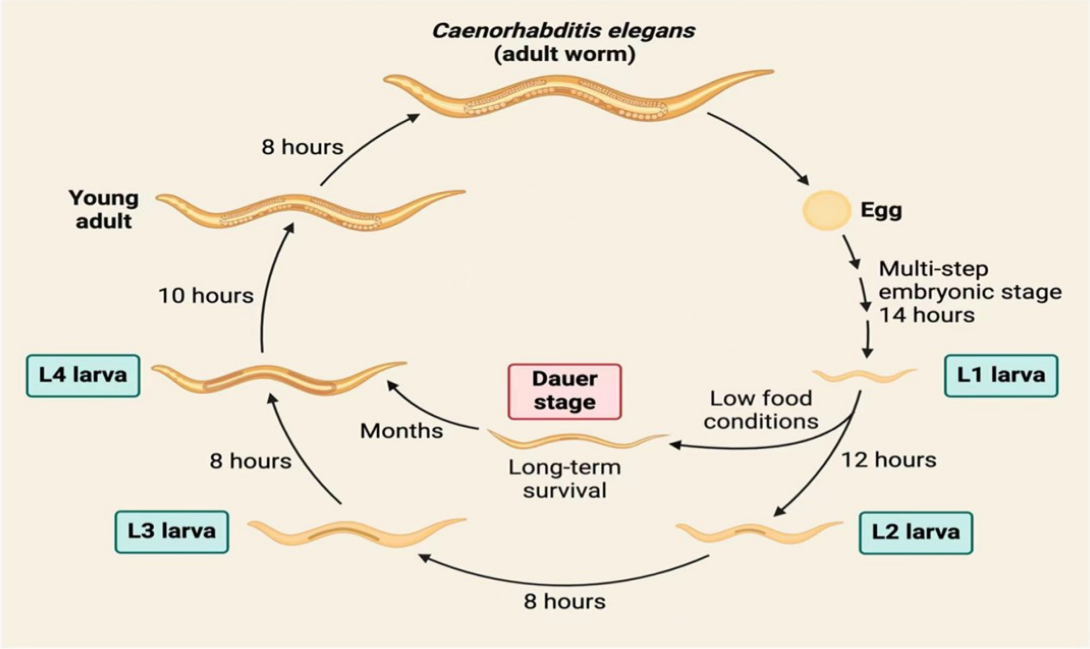


Figure 1. Life cycle of C. elegans [4]

At 20 °C, N2 strain nematodes can go through one full generation every 3.5 days. Along with the long-term survival stage (dauer), which is caused when food is scarce or nonexistent, the key larval phases (L1 to L4) are shown.Compared to other models, C. elegans offers more benefits for researching cause-and-effect linkages between the microbiota and the host. Through the use of microscopy, the colonisation of microbes within C. elegans can be directly observed. Specifically, its usefulness as a model organism for microbiome research is improved by a variety of well-established life history readouts relevant to the impacts of C. elegans–microbe interactions, such as those pertaining to stress tolerance, chemotaxis, foraging behaviour, population expansion, and fertility.

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2.2. Limitations

Despite their utility, animal models face clear limitations in their predictive validity for individual disorders. The gap between human patients and animal models of their diseases is often insurmountable[5].

For example, the pathogenesis of coronary heart disease (CHD) in humans is influenced by long-term adverse lifestyle choices, genetic factors, and the unique structure and function of the human cardiovascular system. While studying mouse models can help identify disease-inducing factors and inform treatment plans, these models may not fully replicate the complexity of the human condition.

The use of animal models to forecast human toxicity has another drawback. About 20% of the 76 animal studies reviewed in 2006 were found to be refuted in humans, and only 37% of them were ever repeated in humans. Comparably, an analysis of 221 animal trials discovered that, in human investigations, agreement occurred only 50% of the time — basically at random.

This inconsistency means that some drugs deemed safe in animals may still cause toxicity in humans.

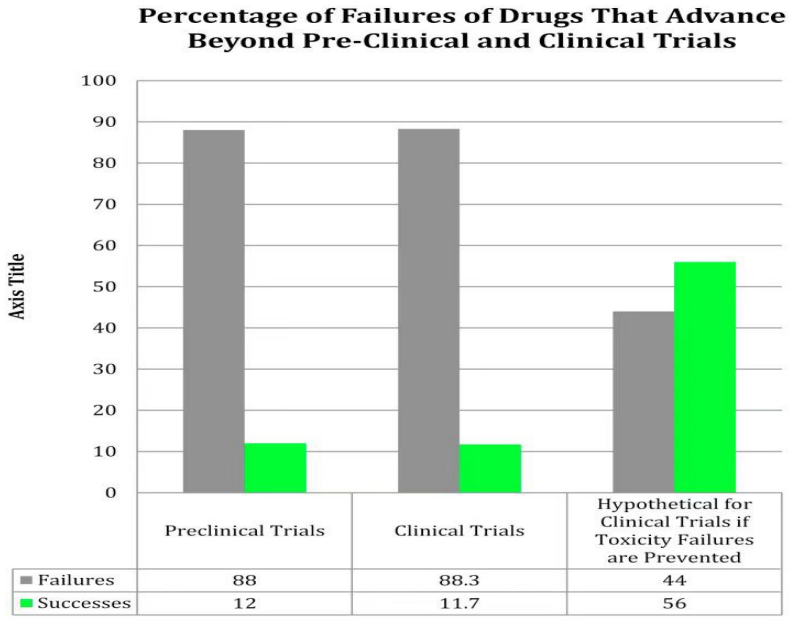


Figure 2. Failures in Translational Research: Preclinical and Clinical Trials[6]

Columns 1 and 2 display the percentages of medications that fail in preclinical trials (because of drug toxicity or ineffectiveness in animal testing) and clinical trials (because of drug toxicity or ineffectiveness in human testing). As half of all drug failures in clinical trials are due to toxicity issues despite safety in animals, the third column illustrates what would happen if there was a strong correlation between the toxicity of animals and humans, leading to the elimination of drugs with human toxicity during the preclinical testing stage through animal toxicity testing. Clinical trial success rates rise from an overall 11.7% to almost 56% [6].

3. Metabolic Syndrome

3.1. Metabolic syndrome

Metabolic syndrome refers to a combination of several complex health conditions involving the body's metabolism of essential substances like proteins, fats, and carbohydrates. It manifests through a variety of symptoms, including abdominal obesity, elevated blood pressure, and abnormal blood sugar levels. For example, a large waist is often a sign of abdominal obesity. Besides, blood pressure persistently above the normal range and elevated fasting blood glucose are also manifestations. In terms of blood

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lipids, triglycerides may increase and HDL cholesterol may decrease. Metabolic syndrome increases the risk of developing chronic diseases such as cardiovascular disease and diabetes, which can seriously affect people's health and quality of life.

3.2. The causes of the metabolic syndrome

- Poor lifestyle: A long-term high-calorie, high-fat diet combined with insufficient exercise can lead to obesity and subsequently cause metabolic disorders. For instance, consuming excessive fried foods and sugary drinks while lacking regular physical activity can contribute to the development of this syndrome.
- Genetic factors: According to relevant research, some individuals are more prone to developing metabolic syndrome due to genetic predisposition. For instance, if there is a history of metabolic syndrome in one's family, the risk of developing this syndrome may be elevated [7].
- Age growth: With the increase of age, the body's metabolic function gradually declines, making people more susceptible to conditions like high blood pressure, abnormal blood sugar levels, and lipid imbalances.
- Psychological stress: Prolonged exposure to high levels of stress can disrupt the endocrine system and contribute to the onset of metabolic syndrome.

4. Research progress of animal models in metabolic syndrome

4.1. Inducible model

The inducible model is to induce a specific disease state or physiological phenomenon through a specific intervention of the experimental object in an artificial way. Researchers manipulate animals using physical, chemical, and biological pathogenic elements, causing specific harm to the animal's tissues, organs, or entire body. This results in functional, metabolic, or toxicological effects similar to those observed in human diseases, enabling the development of corresponding disease models. Induced disease animal models can reproduce a large number of disease models in a short time, and can strictly control various conditions to make the replicated disease models suitable for research purposes, so it is commonly used in modern medical research, especially the first choice for drug screening research.

There are some inducible factors.

1) Physical induction: The model can be induced by physical means. For example, in some animal experiments, tumor models can be induced by implantation to study the relationship between tumor-related metabolic changes and metabolic syndrome.

2) Chemical induction: The use of chemical substances is a common induction method. For example, feeding animals a high-cholesterol, high-fat diet can induce a model of metabolic syndrome that mimics the metabolic disorders caused by a poor diet in humans.

3)Biological induction: Disease models can also be induced through biological factors such as bacterial or viral infections. For example, certain viral infections can cause abnormalities in the immune system, which in turn can trigger metabolic disorders.

An example of physical induction is the use of diet to induce obesity. Obesity is caused by the imbalance of food intake, basic metabolism and energy consumption in daily life, and a variety of environmental or physical reasons may lead to obesity. However, in most cases, excessive caloric intake is considered to be the main cause of obesity. Studies have shown that a diet rich in fat leads to weight gain and diabetes in various types of mice and rats. Over the past 20 to 30 years, many studies have described how animals respond to high-fat diets, with some animals having significant increases in body fat content and others being able to resist the weight gain caused by high-fat diets. The scientists found that B6 mice were the best model to simulate the metabolic disorders observed in human obesity. When fed a high-fat diet, these mice exhibit obesity, hyperinsulinemia, hyperglycemia, and hypertension, but remain lean and metabolically healthy on a normal diet [8].

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4.2. Genetic model

Genetic model is a theoretical framework or mathematical expression used to describe genetic phenomena and laws. It usually includes a description of a gene's structure, function, mode of delivery, and how the gene interacts with the environment. Genetic models facilitate the understanding of the genetic basis of biological traits, the prediction of offspring characteristics, the explanation of genetic variation mechanisms, and provide a theoretical foundation for studying genetic diseases.

Types

1) Mendel genetic model

2) Quantitative genetic model

An example of the application of genetic models is found in genome-wide association studies (GWAS), which scan the genomes of large populations to identify genetic variations linked to metabolic syndrome. For example, researchers may find that certain single nucleotide polymorphisms (SNP) are associated with an increased risk of obesity, hypertension or diabetes. In family studies, linkage analysis can be used to identify gene loci related to metabolic syndrome. By analyzing the genetic markers of sick individuals in the family, the possible pathogenic genes can be determined. GWAS can provide a large number of genetic markers, but usually it can only explain a small part of the genetic risk of metabolic syndrome. But the genetic mechanism of metabolic syndrome can be deeply studied by using animal models. For example, through gene knockout or transgenic technology, a mouse model with specific metabolic abnormalities can be created. These animal models allow for the control of environmental factors and enable more comprehensive physiological and biochemical analyses, aiding in the revelation of the pathogenesis of metabolic syndrome.

4.3. Transgenic model

A transgenic model is created by employing transgenic technology to alter the genes of existing organisms, facilitating the study of specific diseases or biological characteristics. This technology can accelerate or delay some biological processes by artificially adjusting the genes of organisms, thus helping scientists better understand the pathogenesis of diseases, the interaction between environmental factors and genetic factors [9]. The author uses genetic engineering techniques to insert genes associated with metabolic syndrome into animal genomes so that they overexpress specific diseases in specific tissues or organs. Genetically engineered mouse models (GEMMs) serve as core components in the investigation of various genetic, biochemical, proteomic, histological, and phenotypic features of specific human cancers [10]. For example, insulin related genes and fat metabolism related genes can be introduced into the mouse genome to construct a transgenic mouse model of metabolic syndrome. Observing the changes in transgenic animals enables the study of specific genes' roles in the onset and progression of metabolic syndrome. For example, mice that express the adipocytokine gene may show improved insulin sensitivity and metabolic status, revealing the important function of this gene in regulating metabolism.

5. Discussion

Several challenges remain at the current stage. First of all, ethical issues arise from animal genetic modification (GM) models, which involve concerns about animal welfare. These models require strict adherence to relevant regulations and ethical guidelines. Besides, complexity is a significant challenge. Metabolic syndrome results from the interaction of multiple factors, and transgenic models targeting a single gene may not fully capture this complexity. Last but not least, uncertainty is a concern, as GM technology can produce unintended side effects that may impact the reliability and validity of the model.

6. Conclusion

To sum up, transgenic models undoubtedly play an important role in the study of metabolic syndrome. However, in the process of its application, its advantages and challenges must be fully considered. At the same time, it should be organically combined with other research methods to have a more comprehensive and in-depth insight into the pathogenesis of metabolic syndrome, and then explore

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effective treatment strategies. While the use of animal models in medical research is extensive and vital, certain limitations may hinder their effectiveness and accuracy. For the shortcomings of animal models, the future outlook mainly focusses on improving the accuracy of the model and reducing ethical problems. With advancements in science and technology, the development of animal models is expected to become increasingly precise.

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