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The Causes of Using Animal Model to Understand Human Metabolism

Yanming Guo

Malvern College Qingdao, Qingdao, China
3468326897@qq.com

Abstract. It is ethically impermissible to conduct continuous interventions on humans from birth to old age for the purpose of studying the long-term side effects of a new drug or the function of a gene. Animal models offer us a controllable and operable platform for studying complex metabolic processes in a complete life system, which is impossible to achieve in human research. This paper delves into the rationale, methodologies, and implications of using animal models to understand human metabolism. It explores the theoretical bases, presents experimental cases like the Diet-Induced Obesity (DIO) mouse model, and assesses the value and limitations. By examining the biological similarity, controllability, and translational potential, this paper indicates that animal models are crucial tools; the causes for their uses are rooted in a combination of ethical necessity, biological similarity, and practical experimental advantages, but they cannot perfectly replicate the complex metabolism of humans. The insights gained can be used for future metabolism research, such as obesity and diabetes.

Keywords: animal model, metabolism, obesity, medical ethics

1. Introduction

Nowadays the number of people getting the metabolic disorders such as obesity, diabetes, and cardiovascular diseases increases, posing a growing health burden. Understanding human metabolism is crucial for developing effective prevention and treatment strategies [1]. However, direct research on humans is highly controversial with unethical and technical challenges. Furthermore, human living environments, diets, activities, and emotions are extremely complex and difficult to control. Animal models became indispensable substitutes, bridging the gap between clinical trials and basic biology.

This paper provides the theoretical base and experimental case of using animal models in biomedical research, including the study of metabolism. The causes for their use are rooted in a combination of ethical necessity, biological similarity, and practical experimental advantages. This paper analyzes the basic characteristics of animal models, examines the main types of animal models and their principles and use the experimental case: Diet-Induced Obesity (DIO) Mouse Mode.

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2. Basic characteristics of animal models

2.1. Biological similarity

Animals share many genetic and biological similarities with humans, guaranteeing that most metabolic pathways are the same as those in humans [2]. For instance, rhesus monkeys have about 93% genetic similarities with humans. The higher the genetic similarity, the more accurately it can simulate the human metabolic process and the natural course of disease. For example, type 2 diabetes in humans is often accompanied by insulin resistance, obesity and a decline in pancreatic β cell function. Non-human primates (such as cynomolgus monkeys) will gradually develop a pathological process that is completely consistent with humans if they are fed high-sugar and high-fat feed for a long time; they will first show obesity, then insulin resistance, and finally pancreatic β cells will be damaged, blood sugar will rise, and complications (such as diabetic nephropathy, and retinopathy) will also be highly similar to humans [3].

2.2. Controllability

In human studies, it is extremely hard to control all the variables like genetics, diet and environment uniformly. In animal models, however, we can select animals with specific genetic backgrounds and control the diet with precision (control the composition and intake of protein, carbohydrates and fat). Maintaining a standard living environment (including the temperature, humidity and light). The controlling of variables allows researchers to reduce the impact of individual factors on metabolism. For example, in the experiment of the study of finding the effect of fat on metabolism, researchers can feed experimental animals with a quantitative high-fat diet and keep other variables constant, which is nearly impossible in large-scale human observational studies [4].

2.3. Ethical and practical considerations in human

It is ethically impermissible to conduct continuous interventions on humans from birth to old age—such as controlling their mating or arbitrarily extracting tissues or organs for in-depth analysis—for the purpose of studying the long-term side effects of a new drug or the function of a gene. Such experiments are strictly prohibited on ethical grounds. Animal experiments can be conducted under strictly controlled conditions (e.g., identical temperature, lighting, and diet composition), ensuring that variations in experimental outcomes are attributable to the experimental manipulation (such as a specific drug or genetic modification), rather than to confounding factors. Animal models provide alternative pathways for researchers to do the experiment, avoiding the ethical concerns and providing a more intuitive process.

3. Main types of animal models and their principles

Animal models are the cornerstone for understanding the complex metabolic network of the human body. From tiny zebrafish to highly evolved non-human primates, each model, with its unique principles and value, offers an irreplaceable window for us to uncover the mysteries of metabolic diseases and develop new diagnostic and therapeutic strategies. This section of the article will analyze common animal models and the principles.

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3.1. Main types of animal models

3.1.1. Mice

Mice are the most widely used in the experiment. Especially the C57BL/6J, they have a relatively short lifespan, which allows for rapid observation of metabolic changes [5]. It is possible to study the metabolic changes throughout the entire process from embryonic development to aging within a relatively short period of time (the average lifespan of mice is 2-3 years), which would take humans decades. They are susceptible to genetic modification, which allows the study of specific diseases associated with humans. It is possible to breed mice lacking a specific gene (such as leptin or insulin receptor), thereby directly studying the role of this gene in metabolism. The well-known ob/ob (leptin deficiency) and db/db (leptin receptor deficiency) mice are classic models for studying obesity and diabetes.

3.1.2. Rat

Rats are similar to mice, but they are larger in size. So they can be used in the experiment that requires more blood and tissue samples. For example, in the studies of lipid metabolism and atherosclerosis, the larger blood vessels and organs of rats make it easier to perform invasive procedures and obtain samples for analysis. Common types of experimental rats include Zucker (fa/fa) rats and OLETF rats. The former leptin receptor mutation is a classic model for studying obesity and insulin resistance, while the latter spontaneous cholecystokinin (CCK-A) receptor defect, excessive food intake, gradually develops into obesity and type 2 diabetes [6]. The advantage of the rat model is its large size, which is convenient for surgery and sampling. It is more stable than mice in some behavioral and physiological studies, but its genetic tools and gene-modified strains are not as rich as those of mice, and its breeding cost is slightly higher.

3.1.3. Zebrafish

Zebrafishs have a small size, high fecundity, and transparent embryos that allow for easy observation of metabolic processes in vivo at the early stages of development. As emerging vertebrate models, zebrafish and mammals have a high degree of conservation in metabolic organs (liver, pancreas, adipose tissue) and core metabolic pathways [7]. It is mainly used for large-scale genetic screening and drug screening, as well as for studying lipid metabolism, the developmental origin of glucose homeostasis, liver steatosis, etc. However, it is a poikilothermic animal, and its physiological processes, such as body temperature regulation, are different from those of humans. It is small in size, making it difficult to study the energy balance throughout the body.

3.1.4. Drosophila

Drosophila has a simple genetic structure, but 75% of human disease-related genes are homologous to it, such as those for Parkinson's disease and epilepsy. The adipose organ (fat body) of fruit flies is functionally similar to the liver and adipose tissue of humans, responsible for storing and mobilizing lipids. They have similar lipoproteins (such as apolipoproteins), and fat synthesis and decomposition enzyme systems. It takes about 10 to 14 days for a fruit fly to develop from an egg to an adult. This enables researchers to study the impact of aging, dietary intervention, or genetic manipulation on lifelong metabolic health within a short period of time (several months). It would take several years to complete similar research on mice. Its reproductive capacity is extremely strong: a pair of fruit

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flies can produce hundreds of offspring, quickly generating a large number of individuals needed for statistical analysis at an extremely low cost.

3.2. Principles

The choice of animal model depends on many factors; the research question is the most crucial. The research topic might be the study of basic metabolic mechanisms, for example, the role of a certain gene in liver gluconeogenesis. The research topic may also be the study of metabolic diseases, such as the pathogenesis of obesity, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), and atherosclerosis. The topic could also be dietary and nutritional intervention research, such as how does a high-fat and high-sugar diet induces insulin resistance. The function of a certain prebiotic. After defining the research question, here are three key considerations: Sociological Similarity, Inducibility and Reproducibility, and Practicality and Cost. Take physiological similarity as an example for analysis. The digestive systems of omnivorous animals (such as pigs and miniature pigs) are most similar to those of humans. Rodents (rats and mice) are cecal digesters, which are different from humans [4]. It is highly conserved in core metabolic pathways (such as glycolysis and the tricarboxylic acid cycle), but there are differences in details (for example, HDL in mice is the main lipoprotein, while in humans it is LDL). In terms of energy metabolism and weight regulation, there are species differences in the hypothalamus' control of appetite, fat distribution, and insulin action. The highest quality research usually combines multiple models to enhance the reliability and translational potential of the conclusions.

4. Experimental case: Diet-Induced Obesity (DIO) mouse mode

4.1. Experiment design

The DIO mouse model is a classic example of using animal models to study human metabolism. In this experiment, C57BL/6J male mice at 8 weeks of age (a stage corresponding to young adulthood) are used. These mice are fed a high-fat diet with a fat content ranging from 45% to 60%. Studying obesity and metabolism through a high-fat diet, simulating metabolic problems in humans with excessive fat intake.

4.2. Observation period and metrics

The observation usually lasts about 8-16 weeks. During this time, several metrics are monitored. Weight gain is a primary indicator, as it reflects the overall impact of the high-fat diet on energy balance. Blood glucose levels are measured to assess glucose metabolism, and insulin sensitivity is evaluated to determine the development of insulin resistance, a hallmark of type 2 diabetes. These metrics help researchers to understand how high-fat diets destroy normal metabolic processes, leading to obesity and diabetes.

4.3. Results and implications

The body weight of the DIO mouse model shows a rapid increase compared to the control group. Blood glucose levels may rise, and insulin sensitivity may decline over time. These results reflect the development of obesity and diabetes in the human body, and they provide valuable insights for human studies of these disease mechanisms [5]. For example, researchers can find the response of the pancreas and liver to a high-fat diet can be studied.

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5. Limitations

5.1. Ethical issues and animal welfare

During the experiment, animals also suffer due to metabolic disorders, and there is a constant quarrel between the benefits of animal models for science and the protection of animal welfare. Many people have proposed the development of new models, such as in vitro cell culture, to reduce the use of animal models. The scientific research community also strictly adheres to the "3R" principle (Replacement, Reduction, and Refinement) to use animals as humanely as possible [8].

5.2. Cannot be completely replicated complex diseases

The disease, like advanced pancreatic beta-cell failure in type 2 diabetes, involves genetic, environmental and lifestyle factors that may not be accurately reproduced in animals. Interactions between different organs, systems and chronic diseases are difficult to mimic, which limits animal models. No animal can perfectly imitate human beings. For instance, the metabolic rate of mice is much higher than that of humans, and there may be differences in their diet, hormone regulation and drug response. This is why drugs that are effective in rodents sometimes fail in human clinical trials.

5.3. Simplified models

There are limitations in studying human metabolism with animal models. There are differences in metabolic pathways, enzyme activities and hormone regulation among species. The complexity of human organ systems and the types of diseases are difficult to fully simulate. Moreover, animal models are typically used to study specific disease states (such as induced diabetes), but human diseases are often more complex, involving multiple genes, environmental and psychological factors [3]. Therefore, the extrapolation of animal experiment data to humans should be done with caution and in combination with multi-model validation.

6. Conclusion

Animal models have become an indispensable tool for studying human metabolism; they are similar to human genes, controllable, and can also mimic human metabolic processes, which clinical trials and drug research have helped. The primary causes for using animal models to understand human metabolism are the intersection of biological similarity, the ability to conduct controlled and invasive experiments, and the ethical necessity. This article introduces four common animal models, i.e., mice, rats, zebrafish and drosophila, and one experimental case, Diet-Induced Obesity (DIO) Mouse Model to analyze the effectiveness of using animal models to understand human metabolism. The use of animal models to study human metabolism is an irreplaceable and powerful tool within the scope permitted by ethics, taking advantage of their biological similarities to humans and high genetic controllability to reveal metabolic mechanisms, verify scientific hypotheses and develop new therapies in a complete life system. This article also raises the principle of the choice of animal models. First, define the research question, then consider three main aspects: Sociological Similarity, Inducibility and Reproducibility, and Practicality and Cost. Of course, it is also acknowledged that its shortcomings include ethical issues, and it is difficult to replicate complex diseases. Scientists have also always remained vigilant about its limitations and continuously developed new technologies such as organoids and computer models as supplements. But as long as we expand it a

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little and try to weaken its shortcomings as much as possible, this will allow people to have a high understanding of metabolism and metabolic disorders and contribute to human health.

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