Original Article

A Comprehensive Analysis of Ischemic Brain Injury in Rodent Models That is Pertinent to Clinical Stroke in Actual Humans

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Abstract

The second largest cause of death worldwide and a key contributor to disability among survivors is stroke. All 152 human clinical trials undertaken over the past 22 years found that almost none of the 56 neuroprotective medicines that had shown promise in preclinical testing were massive failures.[1-3] The links between results and underlying vascular variability, physiologic regulation, and usage of the comorbidity model are particularly stressed. In this review, we made an effort to establish a connection between the many clinical stroke disorders that exist in humans and the best rodent stroke models. In addition, the review emphasizes the importance of using a variety of preclinical models to comprehend the pathophysiological mechanisms that underlie stroke and to identify novel, safe, and efficient neuroprotective drugs to address this potentially fatal healthcare issue. We seek to advance translational research for the creation of novel treatments for the acute and subacute periods after stroke by identifying the benefits and drawbacks of animal models of stroke and the flaws of prior clinical studies.

Keywords: Stroke, Rodent models of stroke, Preclinical stroke trials,

INTRODUCTION:

One of the most dangerous neurological disorders is stroke. Cancer and coronary heart disease, it is the second most common cause of mortality in wealthy nations. It is the sixth most frequent cause of death in persons aged 20 to 60, and the third most frequent cause of death for those over the age of 65. [1, 4] The sudden loss of brain cells due to insufficient blood supply is known as a stroke, cerebral ischemia, or a cerebral vascular accident.[1,5] Modern stroke pathophysiology is shaped by basic research, which has also uncovered significant molecular, cellular, and systemic factors. However, after decades of study, the majority of translational stroke studies that sought to apply discoveries from basic research to clinical treatment plans, particularly in the area of neuroprotection, fell short.[6] Poor methodological and statistical standards, unfavourable publication bias, and insufficient preclinical testing have all been suggested as "translational barriers," among other challenges. Therefore, it is important to consider how well our stroke models simulate stroke and whether they are designed to respond to clinical queries. Do we need to take into account any flaws in how we interpret the pathophysiological cascades? About 75% of all strokes are ischemic strokes, which are caused by a thrombotic or embolic blockage of a major cerebral artery (often the middle cerebral artery, or MCA), or one of its branches. Clinical research needs very large patient group sizes to minimize the confounding effects of diversity. Clinical variability of stroke is mainly in terms of origins, duration, localization, and severity of ischemia, as well as associated systemic disorders. Experimental models of focal cerebral ischemia have been created to imitate human stroke and are an essential resource in the field of stroke research. Researchers can address particular concerns concerning either pathologic processes occurring after ischemic stroke or how to develop innovative stroke therapeutics in an experimental stroke model by strictly controlling factors.[7] In recent decades, the variety and number of experimental focal ischemia models have grown, and animal studies have largely contributed to our understanding of the pathophysiological processes underlying focal cerebral ischemia.

Since the late 1970s, animal models of cerebral ischemia have been created to pinpoint the mechanisms that lead to tissue damage and provide the groundwork for the creation of novel stroke treatments at the preclinical stage. Recent years have seen the development of several animal models that have been particularly created to address particular risk factors, identify neural repair mechanisms, and test new neuroprotective and recanalizing techniques. Today, a wide range of species, including primates, pigs, sheep, dogs, cats, Mongolian gerbils, rabbits, rats, and mice, are accessible as reliable animal models for stroke. Small animals are really given preference at the preclinical level despite the usage and development of monkey and higher mammal stroke models being a highly essential goal for the following reasons: they work well for ischemic strokes, physiological variables can be monitored sensibly, and enough people can be recruited affordably for statistical study.[8] The rat is the most frequently employed animal in investigations on stroke because of its size, which makes it simple to monitor physiologic factors and handle vascular structures. [9]

WHAT KIND OF ANIMAL MAKES A GOOD STROKE MODEL?

As previously said, it is obvious that there is no perfect animal model of human stroke and that there is much opportunity for advancement in the preclinical experimental stroke study design as it is. When choosing a suitable model for preclinical studies, it is crucial to take the various characteristics of animal models of the stroke into account. The varied character of the disease, the existence of comorbidities, and adequate outcome measures are three factors that are not frequently taken into account in preclinical investigations.

MODELING STROKE'S DIVERSE NATURE:

The varied character of the condition has surely made developing treatments difficult, even though it may not be the only factor in failed translational success and the unfavourable results of the majority of clinical studies in the field of stroke. As previously said, rather than identifying specific patient subgroups, many clinical studies are designed to test a pharmacological drug or a treatment approach versus outcome after stroke in general.[10] The multitude of various models that have been developed reflects the heterogeneity of stroke.[11] Significantly, the cerebral vasculature of most animals, including rodents and large animals, has a high degree of variability comparable to that of humans.[11, 12] However introgressed animal variants, such as the C57BL/6 mouse strain, various rat strains, or gerbils, exhibit significant variation in the structure of their cerebral vasculature, which affects their vulnerability to stroke.[13-15] As a result, there may be some similarities between inter-strain variability and inter-species variability, and variation in human anatomy.[11]

THE TWO PRIMARY GROUPS OF STROKE MODELS ARE:

1. Models of atherosclerosis, hypercholesterolemia, hyperhomocysteinemia, arterial hypertension, and single-gene disorders associated with stroke-like CADASIL are used to study how risk factors (both environmental and genetic) may contribute to vascular damage that ultimately results in stroke. Therapeutical methods to prevent stroke events are also used.[8, 9]
2. Models for investigating the pathophysiological effects of stroke and evaluating treatment options (reanalyzing, neuroprotective and neuroreparative approaches). Models of focal and global cerebral ischemia further differentiate these later categories. To study the processes of cell death and test novel medications as regenerative, neuroprotective, neuroregenerative, and anti-inflammatory therapies, animal models of tissue injury in stroke are created to produce reproducible infarcts in a high throughput way with minimal surgical modification.[8, 9]

The many ways to cause strokes in rodents are a reflection of the complexity of the illness and the necessity for multiple paradigms to facilitate the investigation of therapy strategies.

MODELS TO INVESTIGATE HOW RISK FACTORS (BOTH ENVIRONMENTAL AND GENETIC) MIGHT BE INVOLVED IN THE DEVELOPMENT OF VASCULAR INJURY, WHICH EVENTUALLY RESULTS IN STROKE:

As atherosclerosis develops and progresses, there is mounting evidence that an inflammatory process plays a key role. This process also underlies the etiology of cerebral and heart ischemia.[16,17] Multiple pathogenic mechanisms may culminate in an acute ischemic stroke. Due to the possibility of genetic effects on each of them, it is challenging to establish the traditional patterns of inheritance.[16] Multiple genes may interact and regulate the impact of other risk factors, such as food, smoking, or another gene, or they may have a synergistic effect and increase disease risk in an additive or multiplicative fashion (a gene dose effect).

MODELS FOR STUDYING THE PATHOPHYSIOLOGY OF STROKE AND ITS TREATMENTS:

Models for experimental ischemic stroke

Selection of animals:

The majority of investigations on stroke are now done on tiny animals like rats and the mouse, even though the earliest scientific understanding of the disease came from bigger species. When opposed to larger animals, using tiny animals for stroke research investigations offers benefits in terms of lower costs and more ethical acceptability. The rat is the most frequently utilized animal in studies on strokes for a variety of reasons, including its cerebrovascular anatomy and physiology's similarity to that of humans, [7,18] its manageable size, which enables simple physiologic parameter monitoring and examination of brain tissues,[19] the rather homogeneous nature of strains and, most importantly, the simplicity of carrying out reproducible studies.[20] Since the mouse is the best animal to utilize for genetic manipulation,

transgenic technology is frequently used in research on the molecular pathophysiology of stroke.[21, 22] However, because of their gyrencephalic brains, non-human primates resemble humans more in terms of behavior and sensorimotor integration. Before moving on to clinical trials, it is advised that after a drug study in small animals yields positive results, the investigation be repeated in higher species.[23]

CHOOSING A MODEL

For the majority of animal stroke models applied to clinical situations, cerebral ischemia within the MCA area was induced.[24,25] Permanent or temporary ischemia may be modeled in animal stroke research. The size of an ischemic lesion changes significantly with ischemia time.

CORRELATION BETWEEN ISCHEMIC BRAIN INJURY IN RODENTS AND CLINICAL PROBLEMS IN PEOPLE:

Rodents are especially helpful and appropriate for experimental research of stroke for several reasons: 1) They are easy to handle, anesthetize, and operate on 2) Their cost is reasonable, 3) Their anatomy and physiology are well-known and similar to those of humans, 4) Their brain vasculature is similar to that of humans, 5) they breed prolifically, require little space, and are simple to maintain, 6) Their tissues can be easily obtained, stored, and investigated at relatively low cost, 7) Genetic manipulations are feasible, especially in mice. [7] It is challenging to create a single perfect animal model where the majority of the ischemic stroke can be researched due to the variability of human ischemic strokes. Researchers have the option to choose the best stroke model based on the objectives of the experiment thanks to the diversity of models that are now accessible. The most pertinent models are those of solitary middle cerebral artery occlusion (MCAO) or occlusion of the arteries in the MCA region because human ischemic stroke is frequently brought on by occlusion of the middle cerebral artery (MCA) or one of its branches. Therefore, endovascular or surgical animal models of MCAO are frequently used in investigations that examine the pathophysiology underpinnings of focal cerebral ischemia or test novel neuroprotective medications.[7]

DISCUSSION

Stroke or cerebral ischemia not only has an impact on public health but also poses a significant hazard due to the social and financial costs it causes. It is concerning because low- and middle-income countries have greater incidence, death, and DALY rates. To both prevent strokes from happening in the first place and to treat their effects, new neurotherapeutic drugs are urgently needed. However, stroke remains to be a major unanswered concern for both neuroscientists and clinicians despite the hopeful outcomes from preclinical investigations. Since t-PA was approved in 1996, thousands of neuroprotective medicines have succeeded in experimental tests, but no new medication has demonstrated efficacy.[1] The disparity between human stroke and animal models reveals the success of preclinical research and the failure of clinical trials. Our knowledge of the epidemiology and pathophysiology of stroke has improved thanks to the research we have done in the past, but we should now concentrate on well-thought-out strategies, such as how to prevent reperfusion injury and which drug delivery method is better for treating multiple targets in the brain: a single drug or a combination of drugs. Increased blood regeneration and higher rates of survival for neurons in the penumbra area should both result from the unique strategy. Clinical trials are currently being conducted on several substances that may deliver on the promises of neuroprotection. Drugs should be reevaluated in light of animal studies before moving on to clinical trials. It is important to create awareness campaigns, particularly in developing nations, to encourage stroke victims to routinely attend medical facilities. It has been frustrating to transfer bench success to the bedside. Despite the success of preclinical trials, it is still necessary to develop animal models that closely resemble human diseases to better the transfer of findings from preclinical studies to clinical practice.

CONCLUSION:

The best stroke research model takes into account several variables. The ideal model should have a sufficient number of characteristics that are comparable to those in humans to enable the study of the biological, behavioral, and physiological factors of the pathology so that, after inducing the pathologic process, the outcomes can be investigated and treated with the fewest restrictions possible. Rodents and lagomorphs are the most useful animal models for studies on stroke. These models meet all of the prerequisites that are necessary to create, control, and treat human diseases. However, comparable studies should continue to examine additional models. Preclinical studies are still very helpful despite the variations in the methods utilized and the developmental phases used to simulate humans developing ischemic strokes. They show us that numerous variables affect how functionally people recover from injuries.

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Conflicts of interest

There are no conflicts of interest between the authors.

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