Neurological Testing Following a Stroke in Nonhuman Primates and Models of Ischemic Stroke

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Abstract

Rodents are more similar to humans than nonhuman primates in terms of genetics, neuroanatomy, physiology, and immunology. Therefore, nonhuman primates are regarded as the best preclinical model for simulating numerous elements of human stroke. Nonhuman primates' ischemic stroke models can better mimic the physiological signs and modifications that occur in people after cerebral ischemia. Stroke models in nonhuman monkeys have currently been constructed using a variety of techniques, including craniectomy models, endovascular stroke models, autologous thrombus models, and intraluminal filament models. In the meantime, fresh, novel approaches have been developed, including the photothrombosis and endothelin-1 models. These model studies have investigated numerous pathways that start in the first few minutes, hours, and days following a stroke throughout the past thirty years. In an effort to mimic the intricate circumstances surrounding a stroke, models of both permanent and temporary middle cerebral artery occlusion have been developed. However, it is difficult to do a thorough assessment of the aforementioned techniques' benefits and drawbacks, levels of complexity, and potential application areas. Here, we discuss the numerous modelling approaches that are now available for nonhuman monkey stroke models, contrast the variations among these diverse techniques of preparation, and evaluate the benefits and drawbacks of the various approaches and their areas of application. Also briefly mentioned are the nonhuman primate imaging detection methods for cerebral ischemia and the neurological evaluation procedures for stroke. Scholars can select acceptable modelling and assessment approaches to create nonhuman primate stroke models by sorting and comparing various methodologies.

Keywords: Nonhuman primates • Ischemia stroke • MCAO • Neurological evaluation

Introduction

Strokes affect 15 million people annually, killing 5 million individuals and leaving another 5 million permanently disabled. More than half of stroke survivors over 65 have reduced mobility, making stroke the leading cause of long-term disability in the United States [1]. Ischemic stroke now makes up over half of all stroke cases and is the leading cause of death and disability in people who are not receiving appropriate treatment [2]. The cerebral aorta or one of its branches can become thromboembolic and occlude, resulting in a stroke. Vascular blockage causes hypoxia and energy loss, followed by the production of reactive oxygen species, glutamate release, intracellular calcium build-up, and the initiation of inflammatory processes [3]. Eventually, the brain tissue in this region suffers irreparable harm. The use of thrombolysis and neuroprotective medications are the primary therapy strategy.

However, there are very few thrombolysis medications that are currently licenced and that can be utilised for acute ischemic stroke. Recombinant tissue plasminogen activator is the only medication approved for use in stroke by the Food and Drug Administration (FDA) (rt-PA). The application is essentially invalid and will raise the risk of haemorrhage if it takes longer than 4.5 hours [4]. As a result, 90% of patients are unable to receive thrombolytic therapy in a timely manner. Therefore, it is crucial to either create new thrombolytic medications or increase the duration of action of already existing ones. The use of suitable animal thrombosis models is necessary for the development of novel thrombolytic medications. Rats and mice are frequently used in medical research to evaluate cerebral ischemia due to their affordability, availability of resources, and ease of usage [5]. Although numerous therapy approaches have been demonstrated to be effective following a stroke in rodents, clinical translation has not proven successful. The large variations between human and rat brains, which cause rodents to react differently to the same ischemia damage, are the primary cause of the failure. The structure of the brain and blood vessels, risk factors for cerebrovascular illness, and behavioural traits of large animals (such as pigs, dogs, and nonhuman primates) are similar to those of humans [6]. Therefore, the aetiology and clinical signs of stroke in humans are more similar to those in large animals. Larger brain tissue is suitable for sophisticated surgical procedures and makes postoperative imaging evaluation easier since varied volumes of white matter and grey matter result in different sensitivity to cerebral ischemia. Large animals, particularly Nonhuman Primates (NHPs), exhibit similar neurological damage following stroke, making them excellent candidates for studying the rehabilitation and therapy of stroke. Large animal research does, however, have several drawbacks, including high costs, ethical concerns, and the need for rather advanced testing apparatus. As a result, choosing the best experimental animal to research stroke from among the many available options is exceedingly challenging. Rodents and nonhuman primates (macaques, baboons, etc.) are more similar to humans in terms of physiological makeup and brain blood artery supply. The main application fields of nonhuman primate models are now constrained by economic and ethical considerations. The aetiology and recovery of the treatment, particularly for major illnesses that now have a negative impact on human health, such as human virus infections, respiratory disease, diabetes, stroke, and neuroprotection, have been significantly improved by researchers utilising NHP models [7]. The greatest option for researching human stroke disease is now cerebral ischemia stroke models in NHPs since they can more accurately mimic the physiological signs and modifications that occur in humans after cerebral ischemia. The distribution area of the Middle Cerebral Artery (MCA) is also similar to that of humans, and the size of the brain is quite suitable for Magnetic Resonance Imaging (MRI) research; therefore, numerous scientists have used nonhuman primates to simulate human brain disease [8].

Because NHPs have an intelligence quotient, they are frequently employed in neuroscience to produce ischemic stroke models (mostly the macaque and baboon). NHPs are able to use a variety of tools and perform motor tasks by using their arms. The assessment of neurological function in an ischemic stroke model can be more comparable to that in actual clinical patients because of their level of compliance and irritation following training [9]. As a result, more NHPs are being used in research on various post-stroke treatment options, including acute and long-term pharmacological therapies as well as stem cell therapies following cerebral ischemia. After developing the model, researchers then utilise imaging and neurological behavioural tests to assess the effects of the therapy [10]. There are numerous cerebral ischemia models for MCA because it is a common location for cerebral ischemia in people. Currently, there are several different ways to create NHP models of local cerebral ischemia, including the transcranial approach method, the balloon compression model, the snare ligature model, etc. Stroke can be caused by a variety of mechanisms, but the relevant research area varies.

This article briefly explains the benefits and drawbacks of numerous NHP models of focal cerebral ischemia and briefly presents their modelling methodologies. This research simultaneously sorted the evaluation approach for imaging and neurological function in NHPs following cerebral ischemia based on the model preparation results.

Conclusion

The use of NHPs in medical research is currently restricted due to ethical and financial considerations. Therefore, it's crucial to pick the right model methodologies for research when employing NHPs to examine stroke models. This article primarily discusses the various techniques currently employed for creating cerebral ischemia models in NHPs and quickly assesses, compares, and contrasts their benefits and drawbacks. For the investigation of ischemia-reperfusion injury, secondary oedema, and ischemic penumbra, the craniotomy clamp method and the interventional embolization approach that can control the time of blood flow blockade are suitable. The study of neurological abnormalities brought on by long-term cerebral infarction is better suited to the use of electrocoagulation and other techniques to permanently stop blood flow. The photo thrombosis model was developed in order to simulate the effects of intermittent blood flow blockage and the symptoms of intermittent blood flow reduction in human vascular stenosis. To research thrombolytic medicines, use the autologous thrombus model. The assessment of neurological impairments in NHPs following stroke and imaging evaluation methods is also crucial. In accordance with the experiment's goals, researchers must select the best procedure. Even though there are numerous additional animal models that are utilised for studying strokes, the majority of clinical translations are unsuccessful. Newer and more potent therapies must be translated from the laboratory to the bedside for patients with ischemic stroke.

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