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REVIEW ARTICLE

Animal models of stroke

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Abstract

Stroke is a devastating disease with high morbidity and mortality. Animal models are indispensable tools that can mimic stroke processes and can be used for investigating mechanisms and developing novel therapeutic regimens. As a heterogeneous disease with complex pathophysiology, mimicking all aspects of human stroke in one animal model is impossible. Each model has unique strengths and weaknesses. Models such as transient or permanent intraluminal thread occlusion middle cerebral artery occlusion (MCAo) models and thromboembolic models are the most commonly used in simulating human ischemic stroke. The endovascular filament occlusion model is characterized by easy manipulation and accurately controllable reperfusion and is suitable for studying the pathogenesis of focal ischemic stroke and reperfusion injury. Although the reproducibility of the embolic model is poor, it is more convenient for investigating thrombolysis. Rats are the most frequently used animal model for stroke. This review mainly outlines the stroke models of rats and discusses their strengths and shortcomings in detail.

KEYWORDS
animal models, cerebral hemorrhage, ischemia, stroke

1 | INTRODUCTION

Stroke is a leading cause of morbidity and mortality worldwide and in China. In China, stroke was the leading cause of death and DALYs in 2017.[1] Age-standardized DALYs per 100 000 population decreased by 33.1% for stroke. Of all strokes, up to 80% to 85% are ischemic,[2] which can be subdivided based on the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.[3] Large vessel atherosclerosis of cervical or proximal intracranial vessels comprises a major cause of acute stroke, ranging from 30% to 43%, while 20%-31% is caused by cardioembolism. Approximately 10%-23% of all strokes are lacunar in type, which are mainly caused by diabetes and hypertension. Some additional unusual causes, such as vasculopathy or extracranial artery dissection, account for 2%-11%.[4,5] Approximately 5%-21% of strokes are hemorrhagic, and their common causes are hypertension and vascular malformations.[6] Strokes are heterogeneous diseases, and in vivo models are essential tools to mimic these processes for investigating pathophysiology and therapeutic approaches. Each model has its unique strengths and weaknesses (Tables 1 and 2). Only when we realize their importance can we choose the best one for an investigation, with "best" referring to that which most closely approximates a certain aspect of the multiple facets of strokes.

2 | ISCHEMIC STROKE

Tissue plasminogen activator (tPA), adapted from a rabbit model,[7] is the only therapeutic agent approved to treat acute ischemic stroke.[8] From the late 1970s, a variety of animal stroke models have been

TABLE 1 The characteristics of stroke models

Models	Advantages	Disadvantage	Animals
Ischemic stroke			
Global ischemic stroke			
4-VO model	Easy to prepare; high reproducibility; low incidence of seizures	Two-stage surgical procedure; permanent occlusion vertebral arteries; high mortality	Rats, mice, rabbits, dogs, pigs
2-VO model	One-stage surgical procedure; controllable recirculation; lower mortality	Poor reproducibility; strains-depended	Rats, mice, rabbits, cats, dogs, sheep, pigs
Complete global brain ischemia	Close to human condition of cardiac arrest and resuscitation	Extracerebral complications; complicated procedure; poor survival rate and coma	
Ventricular fibrillation cardiac arrest			Rats, rabbits, cats, dogs, pigs, sheep
Aorta/vena cava occlusion models			Dogs and pigs
Chemical and gas hypoxia			Zebrafish
Focal ischemic stroke			
Transcranial occlusion	Smaller infarcts; lower mortality; high reproducibility	Destroy dura; intracranial infection; one-sided blindness	Rats, mice, cats, sheep, pigs, monkeys
Endovascular filament occlusion	Easy manipulation; controllable reperfusion; ischemic penumbra	Tremendous variations; spontaneous hyperthermia; not suitable for thrombolysis	Rats, mice
Embolic occlusion			
Thromboembolic occlusion	Investigate thrombolytic processes	Poor reproducibility; spontaneous recirculation	Rats, rabbits, dogs
Artificial spheres occlusion	Microspheres induce graded infarcts; reproductivity of macrosphere embolization	Poor reproducibility of microspheres models; not suitable for transient occlusion and thrombolysis	Rats, rabbits, primates
Endothelin-1 occlusion	Easy manipulation; flexible selection of infarct regions	Affected by anesthetics; neural transmission/ modulation	Rats
Photothrombosis model	Reproducibility; easy manipulation; less trauma; long-term survival	Lack of penumbra; poor responses to rt-PA	Rats, mice
Intracerebral hemorrhage			
Whole blood injection model	Mimic the hematoma mass effect and blood toxicity	Uncontrollable hematoma size; not suitable for studying bleeding and hemostasis	Rats, mice, rabbits, pigs
Collagenase model	Spontaneous bleeding; easy manipulation. The size of hematoma is controllable.	Bleeding is slow and diffuse. exacerbates the inflammatory response	Rats, mice, dogs, pigs

developed with the aim of identifying the mechanisms of and developing new agents for ischemia therapy.[9] However, no preclinically tested agents have been translated into effective stroke therapies,[10] which led to the establishment of the Stroke Therapy Academic Industry Roundtable (STAIR). It aims to draft recommendations for improving the quality of preclinical studies because we need

ischemic stroke models that are more representative of the human condition.[11] Several recent animal models are known to exhibit cerebral ischemia and have been designed to address specific risk factors. These models can be generally divided into two types, global ischemia model and local ischemia model. Reliable stroke models for ischemia are available in a variety of species, including primates, domestic animals, and rodents.

2.1 | Global ischemic stroke

Compared to global ischemia models, the focal ischemic stroke models are more relevant to the human ischemia.[12] Although global cerebral ischemia is not a common feature, it is also relevant in global brain damage due to cardiac arrest and resuscitation. In addition, a global model of reversible ischemia may be important in identifying the mechanism of potential neuroprotective agents.[13] The global ischemia model, both incomplete and complete, characterized by the critical reduction of cerebral blood flow in the whole brain, tends to be easier to perform. It can be induced by different approaches. The most commonly used ones are the incomplete global ischemic models of the four-vessel occlusion model (4-VO model) and two-vessel occlusion model (2-VO model).

2.1.1 | 4-VO model

In 1979, a 4-VO model was first introduced by Pulsi-Purkinjenelli and Brierley in unanesthetized rats to result in bilateral hemispheric ischemia with highly predictable brain damage.[14] This model consists of a two-stage procedure with permanent occlusion of the vertebral arteries by electrocoagulation on day 1 followed by reversible occlusion of the common carotid arteries (CCA) on day 2.[15] Based on the anatomical basis of vertebral artery proposed by Sugio et al, Toda et al improved the 4-VO model for highly reproducible forebrain ischemia. The vertebral artery at the second vertebra was electrocauterized under microscope to ensure complete occlusion of circulation of both vertebral artery.[16,17] This model shows biphasic changes in brain edema and scavenging activity of superoxide following cerebral ischemia reperfusion.[17] Brain water contents increases at 1-48 hours after recirculation, but are almost equal to the normal brain at 24 hours.[17] The lowest and highest superoxide scavenging activities are found at 45 minutes and 12 hours after recirculation, respectively.[17] The model has various advantages, such as ease of preparation, a high rate of predictable ischemic neuronal damage, and a low incidence of seizures. The major weaknesses are the need for a long time to finish a two-stage surgical procedure and vertebral arteries being permanently occluded. Furthermore, because of the high mortality and common complications, animals require better postoperative care. In addition to rats, other mammals such as pigs,[18] dogs,[19,20] rabbits,[21] and mice[22]have been used.

2.1.2 | 2-VO model

In 1972, the 2-VO model was first proposed by Eklof and Siesjo in lightly anesthetized rats and has been modified on many occasions since.[23] Ligation of the carotid arteries alone decreases cerebral blood flow to approximately half of normal, but it has no significant changes in the energy state of the tissue,[23] which is mainly due to the well-developed circle of Willis in rats.[24] Thus, permanent occlusion of bilateral carotid arteries could produce a model for chronic cerebral hypoperfusion-related neurodegenerative diseases.[25] The changes in CBF can be divided into three phases including acute phase (start of occlusion lasting for a maximum of 2-3 days), chronic hypoperfusion phase (lasting for 8 weeks to 3 months), and restitution phase.[25] However, the second phase is closest to the condition of CBF reduction in human aging and dementia.[25] Although the permanent 2-VO model does not show BBB destruction, there are other changes in pathophysiological processes, such as alteration of electrophysiological activity, neuropathologic changes, and continuous oxidative stress.[25] Transient bilateral carotid artery occlusion (BCAO) should be combined with a reduction in mean arterial blood pressure, which could successfully establish a forebrain ischemic model.[26,27] The insult in size and location produced by this model is similar to that of the 4-VO models, with the exception of the brain stem. By the mid to late 1980s, the 2-VO model gradually replaced the 4-VO model because of its advantages, such as a one-stage surgical procedure, controllable recirculation, and lower mortality.[13] However, the success of the model requires appropriate strains and a precise grasp of the ischemic time. Mortality after BCAO varies from 0% to 100% depending on the strain. Modifying the time interval between the ligations of the bilateral carotid artery could ameliorate lethal effects.[28] The approach is commonly used not only in rats but also in other experimental animals, such as pigs,[29,30] ovine fetuses,[31] neonatal dogs,[32] cats,[33] rabbits,[34] and mice.[22] It is worth mentioning that gerbils and spontaneously hypertensive rats (SHRs) have unique advantages itself.

Most likely, the simplest model is that of BCAO in Mongolian gerbils (*Meriones unguiculatus*). Unilateral or bilateral carotid artery occlusions of gerbils were first described by Levine and Payan in 1966.[35] They are widely used in forebrain ischemia because of the incomplete cerebral circle of Willis. For 5 minutes BCAO of gerbils, the CA1 region of the dorsal hippocampus will undergo an unusual series of changes.[36] According to the severity of transient ischemia, neuronal loss in the hippocampus significantly differs.[37] Due to the low blood volume, the major disadvantage of this model is the difficulty in taking blood samples and monitoring blood gas parameters. In addition, the variability of cerebral vascular anatomy determines the severity of ischemic insults in gerbils.[38] Compared to high oak gerbils, Charles River gerbils have an increased incidence of the complete or partial circle of Willis (38.6% with unilateral anastomoses and 22.7% with bilateral anastomoses).[39]

SHRs were constructed by Okamoto and Aoki in 1963.[40] The resting blood flow values between SHRs and normotensive rats (NTR) were not different. However, after BCAO, the cerebral blood

TABLE 2 The pathophysiological characteristics of stroke models

Stroke models	Common processes	Special characteristics
Ischemic stroke		
Global ischemic stroke		
4-VO model	Energy failure, elevated intracellular Ca^{2+} level, excitotoxicity, spreading depressions, generation of free radicals, destruction of the blood-brain barrier, inflammation, glial cell contribution, apoptosis, and necrosis	Biphasic changes in the brain edema and scavenging activity of superoxide
2-VO model		Permanent 2-VO model shows three phases of CBF changes Permanent 2-VO model does not show BBB destruction
Complete global brain ischemia		
Aorta/vena cava occlusion models		Purkinje cells and the CA1 pyramidal cells induced by CGBI consists of two phases, and the reversible change in the early phase is related to the decrease of the synaptic vesicles
Ventricular fibrillation cardiac arrest		A VF of 5-7 min could be easily recovered with resuscitation, while VF for 10 and 12 min often cannot be recovered Significant ischemic cell changes (eosinophilic cytoplasm, dark-staining triangular shaped nuclei, and eosinophilic-staining nucleolus) in CA1 hippocampus can be observed at seven days of resuscitation
Chemical and gas hypoxia		
Focal ischemic stroke		
Transcranial occlusion	Energy failure, elevated intracellular Ca^{2+} level, excitotoxicity, spreading depressions, generation of free radicals, destruction of the blood-brain barrier (BBB), inflammation, glial cell contribution, apoptosis, necrosis	Leakage of cerebrospinal fluid; one-sided blindness
Endovascular filament occlusion		Spontaneous hyperthermia; unavoidable harm to the endothelial lining could alter vascular reactivity and BBB permeability
Embolic occlusion		
Thromboembolic occlusion		Unreliable infarctions and variable neurologic deficits; mainly to investigate thrombolytic processes Autologous blood clots of experimental animals are resistant to human rt-PA
Artificial spheres occlusion		Microsphere embolization produces relatively variable infarcts Macrosphere embolization model provides focal cerebral infarcts similar to intraluminal suture occlusion but avoids hypothalamic injury and hyperthermia
Endothelin-1 (ET-1) occlusion		Vasoconstriction; ET-1 plays a role not only in local control of cerebral vascular tone but also in neural transmission/modulation. endothelin-converting enzymes and endothelin receptor B are expressed in neurons and astrocytes, and regulated by nerve injury
Photothrombosis model		Photooxygenation leads to endothelial damage and platelet adhesion, and aggregation to form thrombi to block cerebral vessels Classic photothrombotic stroke has poor responses to rt-PA-mediated thrombolysis
Intracerebral hemorrhage		
Whole blood injection model	Hematoma enlargement, coagulation cascade activation and clot retraction, red blood cells lysis and infusion of hemoglobin, brain edema, necrosis and apoptosis, CBF reduction, inflammation	Mimics the hematoma mass effect and blood toxicity; involves no rupturing of cerebral vessels; no activation of bleeding and coagulation cascade
Collagenase model		Mimics bleeding; degrades collagen IV in the basal lamina of the blood-brain barrier; rupture of small vessels and capillary beds around the injection site. Bacterial collagenase exacerbates the inflammatory response

flow in the cortex or thalamus was reduced more in SHRs than in NTRs.[41] Furthermore, BCAO alone could cause severe ischemic insults of the brain in SHRs.[42] Seizures develop within 1 hour in BCAO of awake SHRs.[43] However, high mortality and feeding requirements are the main causes that limit the development of this model. All stroke-prone spontaneously hypertensive rats (SHRSP) died within 6 hours after BCAO. Stroke-resistant SHRs (SHRSRs) and Wistar-Kyoto rats (WKYs) died within 8 hours after BCAO.[44]

2.1.3 | Complete global brain ischemia (CGBI)

The 4-VO models and 2-VO models are incomplete global ischemic stroke models. Other models mainly mimic complete global brain ischemia (CGBI), such as aorta/vena cava occlusion and cardiac arrest. They are very good models for the human condition of cardiac arrest and for resuscitation. CGBI of dogs by ascending aorta occlusion combined with bypass formation between the aorta and right atrium for 18 minutes could result in severe brain damage.[45-47] The damage to the Purkinje cells and the CA1 pyramidal cells induced by CGBI consists of two phases, and the reversible change in the early phase is related to the decrease of the synaptic vesicles.[46] Jackson and Dore modified this model by using aortic and inferior vena cava occlusion balloons, which avoids surgical invasion of the thorax.[48] Because of the great loading of lung circulation, aorta occlusion without vena cava occlusion is more suitable for short-term study on CGBI.[49] Dogs and pigs, as large animals, are the common choices in this model.

Another common scheme to induce CGBI is ventricular fibrillation (VF) cardiac arrest. Briefly, this model is established by VF and follows resuscitation. VF is mainly induced by shocking the heart with electric stimulation. Urgent cardiopulmonary resuscitation may include chest compression, adrenaline injection, transthoracic countershock, and mechanical ventilation.[50] A VF of 5-7 minutes in dogs is easily reversed with resuscitation. Usually, VF of 10 or 12 minutes cannot be reversed. Therefore, a permanent brain damage is inevitable.[51] Significant ischemic cell changes (eosinophilic cytoplasm, dark-staining triangular shaped nuclei, and eosinophilic-staining nucleolus) in the CA1 hippocampus can be observed at 7 days of resuscitation.[50] In addition to rats and dogs, other mammals such as pigs,[52,53] sheep,[54] cats,[55] and rabbits[56] can be chosen.

Aorta/vena cava occlusion models and cardiac arrest models, as common approaches to build CGBIs, can be used to investigate neuroprotective drugs. However, there are several disadvantages that limit the development of such models. The interruption of systemic blood supply leads not only to brain damage but also to a series of extracerebral complications. In addition, complicated procedures, low survival rates and high rates of coma can occur in these models. This means that intensive care should be taken postischemia during the first couple of days.

Blockage of cerebral blood vessels means deprivation of oxygen and nutrients. The brain is extremely sensitive to hypoxia and dies 5 minutes after interruption of the oxygen supply. A special model of GCBI is chemical and gas hypoxia in zebrafish.[57-59] Infarcts can be seen in the optic tectum after 10 minutes of gas hypoxia. With the prolongation of hypoxic treatment, the insult extends to the depth of the optic lobe.[57] This method is easy to use and has advantages in high-throughput screening of stroke drugs, but it can only simulate the hypoxic mechanism of cerebral ischemia.

2.2 | Focal ischemic stroke

Focal ischemia, wherein blood flow is reduced in a very distinct and specific region of the brain, is more relevant to human stroke than global ischemia. Multifocal ischemia reduces brain blood flow in a patchy pattern.[60] Focal ischemic stroke models usually show several common pathophysiological characteristics including energy failure, elevated intracellular Ca^{2+} level, excitotoxicity, spreading depressions, generation of free radicals, destruction of the BBB, inflammation, glial cell contribution, apoptosis, and necrosis which occur after CBF reduction without a certain order.[61] Focal cerebral ischemia models are established by mechanical occlusion vessels or various embolization approaches.[9] At present, this model is mainly divided into five types: transcranial occlusion, endovascular filament middle cerebral artery occlusion (MCAo), embolic occlusion, endothelin-1 occlusion, and photothrombosis model. Because the middle cerebral artery (MCA) is the most frequently involved territory (almost 50%),[4] most models of focal ischemia involve occlusion. MCA occlusion might mainly cause cortex and striatum insults, but the extent of infarction depends on the location and duration of occlusion and the amount of collateral blood of the MCA. Because of their easy manipulation and high survival rate, they have become the most commonly used models in the investigation of etiopathogenesis and novel treatment of ischemic strokes, especially the endovascular filament model.[62]

2.2.1 | Transcranial occlusion

Many animals, such as dogs, pigs and other large domestic animals, have rich collateral circulation (rete mirabile). An effective way to solve this problem is to block the more terminal blood vessels supplying the brain, and transcranial occlusion is a reliable choice.[63] Craniectomy requires the opening of the skull and sectioning of the dura mater to directly block the proximal cerebral artery. There are two main methods to build the model, including occlusion of the proximal MCA alone by direct electrocoagulation, ligation, transection, and photothrombosis,[64-69] and combined occlusion of the MCA and bilateral common carotid artery (three-vessel occlusion model, 3-VO model) or ipsilateral common carotid artery.[70-72] The techniques permit permanent and transient occlusion, which depend on the blocking time. In the first method of modeling, the frontal cortex and lateral part of the neostriatum are commonly involved,[64] but the size of lesions is strain dependent.[73] Occlusion MCA and common carotid artery mainly result in infarction of the ipsilateral neocortex

in the MCA territory,[74] and infarct size also varies by strain.[75,76] The first method is widely used in rodents,[64-66,68] large domestic animals,[77-80] and primates.[81] In addition, the second models are commonly used in rats. Compared to suture-based MCA occlusion models, transcranial occlusion models induce smaller infarcts, lower mortality, and higher reproducibility.[63] However, craniectomy destroys the integrity of the brain environment, which not only causes leakage of cerebrospinal fluid but also increases the possibility of intracranial infection. If the transorbital approach is used, an inevitable side effect, one-sided blindness, will occur. This would affect the detection of postoperative neurological deficits. Furthermore, it requires a certain degree of surgical technique.

2.2.2 | Endovascular filament middle cerebral artery occlusion (MCAo)

The most common method of focal ischemic stroke is intraluminal thread occlusion of the MCA, which has been used in more than 40% of stroke research.[62] The model was first described by Koizumi et al in 1985 and modified by Longa et al in 1989.[82] The basic technique involves introducing a filament with a round tip from the external carotid artery (ECA) into the internal carotid artery (ICA) and advancing it to block the origin of the MCA.[83] On this basis, ligation of the distal branch of the ICA around the intraluminal filament can produce a more reliable infarct model.[84] The model can be used to establish permanent or transient focal cerebral ischemic stroke depending on variable reperfusion time points.[75,85] As the time of occlusion elapses, it will lead to gradually serious brain insults. One hour after occlusion, the ischemic cell change is slightly scattered, whereas occlusion for more than 3 hours causes severe ischemic lesions in the anterior neocortex and the lateral part of the caudate putamen supplied by the MCA.[86] After permanent MCA occlusion, irreversible injury appears first in the caudoputamen and then spreads to the cortex.[87] In addition to the abovementioned factors, transient and permanent MCA occlusion exhibits tremendous discrepancies in various pathophysiological processes, such as neuronal apoptosis, neuroinflammation, and oxidative stress.[88]

Although this approach avoids the inconvenience of craniotomy, the size and distribution of ischemic infarcts vary considerably among laboratories. The selection of strains, the properties of filaments, and the location of occlusion play key roles in the generation of these variations. Sprague-Dawley rats are commonly used for intraluminal filament occlusion, but they are not the most appropriate strain. Compared to its effects on Sprague-Dawley and Wistar-Kyoto rats, intraluminal MCA occlusion in SHRs is associated with a more severe and reproducible volume of ischemic lesions.[89-91] Furthermore, not every strain is suitable for filament MCA occlusion due to the discrepancy of cerebrovascular anatomy,[92,93] and the Fischer-344 rats and SV129 mice show this very well.[94,95] The types of sutures significantly influence the final infarct volume. Compared to uncoated filaments, filaments coated with silicone, poly-L-lysine, or paraffin increase ischemic lesions and reduce interanimal variability.[96-100] Other small changes in sutures also affect reproductivity in this model, such as the diameter of the suture tip and the insertion distance of the suture.[101,102] However, the application of electrocorticography (ECG), laser Doppler flowmetry (LDF), and magnetic resonance imaging (MRI) can effectively guide filament placement, reduce the variations caused by the insertion distance, and immediately identify subarachnoid hemorrhages and premature reperfusion.[103-105]

Except for the tremendous variations among laboratories, the model has other shortcomings. Almost half of all rats experienced ECA ischemia detected by MRI. The adverse effects of ECA ischemia potentially impacted the outcome of this model.[106,107] Proximal MCA occlusion results in a massive infarct. Involvement of the hypothalamus leads to spontaneous hyperthermia,[108] which may worsen the outcomes and obscure neuroprotective effects.[109] Furthermore, it is impossible to simulate thromboembolism under human conditions by intraluminal filament occlusion. Thus, it cannot be used in thrombolysis research. The main weakness is the unavoidable harm to the endothelial lining of the ICA, which will be exacerbated by reperfusion. This injury could alter vascular reactivity and BBB permeability. However, its lack of craniotomy, ease of manipulation, accurate control of the ischemic duration, and the presence of a significant ischemic penumbra may be the main factors leading researchers to choose this model. With the development of transgenic and knockout mice, this model has been widely used not only in rats but also in mice.[110]

2.2.3 | Embolic occlusion

Most focal ischemic strokes are caused by thromboembolism. Embolic occlusion models can match this specific condition better, which permits us to investigate the mechanism of vascular occlusion. Embolic occlusion falls into two main categories: thromboembolus and artificial spheres. Thromboemboli can be further divided into spontaneous blood clots (autogenous or allogeneic blood clots)[111,112] and induced thrombi (thrombin-induced clots and photothrombosis).[113-117]

In 1982, Kudo et al first described thromboembolic occlusion in rats created by intracarotid injection of homologous blood clots.[111] The surgical approach was essentially the same as the intraluminal filament occlusion model. The infarct predominantly involved the blood supply territories of the middle cerebral artery and anterior choroidal artery. The distribution of infarcts was wide and uncontrollable, including the parietotemporal cortex, hippocampus, thalamic striatum, and even a small proportion of the contralateral hemisphere.[111] In particular, in line with human ischemic stroke, except for the time of occlusion, the time of spontaneous recirculation of the thromboembolic model is also uncertain.[118] Late recanalization occurs in most patients with ischemic stroke, and early reperfusion may lead to limited infarcts in the transient ischemic attack. In the experimental situation, premature recirculation diminished the difference in lesion extent

between thrombolytic-treated animals and controls. Unreliable infarctions and variable neurologic deficits can be modified by precise occlusion MCA utilizing microcatheter and LDF.[119,120] The main application of the thromboembolic model is to investigate thrombolytic processes. However, the response of the thromboembolic model to rt-PA is different and highly depends on the composition and volume of emboli. The efficiency of thrombolytic therapy is related to the number of red cells and inversely related to the volume, fibrin content, and density of embolic blood clots.[121] Thrombin-induced clots are classified as elastic and fibrin-rich, and spontaneously forming clots are classified as plastic. Compared with thrombin-induced clots, spontaneously forming clots have a faster response to rt-PA.[114] In addition, autologous blood clots of experimental animals are resistant to human rt-PA. Under comparison conditions, human rt-PA can dissolve over 95% of human plasma clots in vitro, but 80% of primate plasma clots, 60% of cat and rabbit plasma clots, 30% of dog plasma clots, and only 10% of rat plasma clots.[122] Therefore, most thrombolysis studies in rats use 10 mg/kg rt-PA instead of 0.9 mg/kg, which is the common clinical dose in ischemic stroke patients. The cumulative reperfusion flow induced by 0.9 mg/kg rt-PA was only one-half that induced by 10 mg/kg rt-PA. In addition, 10 mg/kg rt-PA was more effective than 0.9 kg/ml rt-PA in reducing the degree of brain edema. In addition, rats treated with 0.9 and 10 mg/kg rt-PA exhibited differences in mean reperfusion times of 40 and 25 minutes but showed similar reperfusion slopes. These data show that the differences of 0.9 and 10 mg/kg rt-PA result from a slower effect of 0.9 mg/kg rt-PA at starting reperfusion due to the relatively low sensitivity of the rat's fibrinolytic system to rt-PA.[123] Thromboembolic models are widely applied not only in rats but also in domestic animals such as rabbits and dogs.[124-126]

In addition to thromboembolus, an embolic occlusion model can be induced by directly injecting artificial microspheres (15-50 μm) or artificial macrospheres (300-400 μm diameter) into the CCA, ICA, or MCA, most commonly not only in rats,[127,128] but also in large animals and primates.[129-131] Artificial microsphere embolization is characterized by widespread infarcts in the parietotemporal cortex, corpus callosum, hippocampus, thalamus, and lenticular nucleus of the embolized hemisphere.[127] The development of infarct lesions can last for 24-48 hours, which is significantly slower than that of the intraluminal filament model.[132] Primarily developed to mimic transient ischemic attacks and cerebral microcirculatory disorders,[133,134] it can also be used to induce graded infarcts depending on the number of emboli.[130] Microsphere embolization produces relatively variable infarcts, which requires more animals to be used to test neuroprotective agents for a statistically significant result. Unlike microsphere embolization, macrosphere embolization is more reproducible and reliable. The macrosphere embolization model provides focal cerebral infarcts similar to intraluminal suture occlusion but avoids hypothalamic injury and hyperthermia.[128] However, the model is only suitable for producing a permanent model but temporary occlusion and cannot be used for thrombolysis research as can the intraluminal thread model.

2.2.4 | Endothelin-1 occlusion

Endothelin-1 (ET-1), a 21-amino acid peptide with potent vasoconstrictor properties, was first described in 1987.[135] Local application of ET-1 to vessels can cause a significant reduction in cerebral blood flow, which is severe enough to induce ischemic injury.[136] Directly administrating ET-1 to the surgically exposed MCA markedly reduces CBF of the caudate nucleus, the genu of the corpus callosum, and the cortex lying wholly within the territory of the MCA.[137,138] Similar infarct volumes can be achieved by injecting ET-1 into the superficial cortex of conscious rats via a stereotaxic guide cannula adjacent to the MCA.[139,140] In addition to the above applications, stereotactic injection of ET-1 into the cortex can be used to induce infarction in other specific brain regions, such as internal capsule ischemia and frontoparietal cortex infarction.[141-143] The application of ET-1 can produce a permanent or transient cerebral infarction, which depends on the dosage of ET-1 to a large extent. The reduction of CBF can be completely reversed within 4 hours for the lower doses of ET-1 but only partly reversed at 25 μL of 10^{-5} mol/L. Reversible occlusion with ET-1 incorporates initial profound ischemia and the second stage of increasing reperfusion lesion, which provides evidence of the reperfusion injury.[140] It should be emphasized that the effect of ET-1 on vasoconstriction can also be affected by anesthetics. Compared with conscious rats, anaesthetized rats need approximately four times the dose of ET-1 to produce a similar infarct volume.[144] This model is widely used in rats due to its advantages of easy manipulation and flexible selection of infarct regions. However, it seems that mice are not suitable for this method.[145] The most limited application of this model is that ET-1 not only plays a role in local control of cerebral vascular tone but also plays a part in neural transmission/modulation.[146,147] Furthermore, endothelin-converting enzymes and endothelin receptor B are expressed in neurons and astrocytes and regulated by nerve injury.[148,149] Thus, exogenous ET-1 may make the pathogenesis of ischemic stroke more complicated and affect the evaluation of neuroprotective drugs.

2.2.5 | Photothrombosis model

In 1985, the photothrombotic model was introduced by Waston et al to produce a more reproducible cortical infarct without craniotomy in rats.[150] The process of carrying out this model is to inject photosensitive dye (rose bengal, erythrosin B) into circulation and then to irradiate the intact cranium of a specific area with a certain range of wavelength laser beams to induce focal cerebral ischemia. The main mechanism is that dye-sensitized photooxygenation leads to endothelial damage and then platelet adhesion and aggregation to form thrombi to block cerebral vessels. In addition, the rat skull is sufficiently translucent to transmit the effective photochemical intensity to the internal brain regions, which makes craniotomy unnecessary.[150]

In recent decades, the application of this model has been constantly developed and modified to achieve greater specificity. In

addition to photochemical embolization of cortical microvasculature to cause local cortex infarction, the laser beam can directly irradiate a certain vessel to produce cerebral ischemia in its supply regions. Photochemically induced nonocclusive common carotid artery thrombosis is a special thromboembolic model of forming a unilateral carotid thrombus with subsequent platelet embolization in the downstream circulation, which produces consistent and reversible neurobehavioral deficits.[115] Brain injury varies between rats, but the majority of infarcts are observed in the ipsilateral cortex.[116,117] Except for CCA, photothrombosis is commonly used in MCA occlusion with or without craniotomy.[151,152] The infarct volume of MCA photothrombosis varies and is strain dependent.[153] It is not possible to determine the exact time of recanalization. However, based on the mechanism of vasorelaxation induced by a pulsed UV laser,[154] photochemical MCA occlusion and reperfusion can be controlled by utilizing a 2-laser system.[155,156] Classic photothrombotic stroke has poor responses to rt-PA-mediated thrombolysis, which may be due to the platelet-rich and fibrin-poor composition of blood clots. The modified photothrombosis is rose bengal plus thrombin, which can produce mixed platelet:-fibrin clots and enhance the sensitivity to rt-PA treatment.[157] In addition, it has been proven that some details of the procedure can be refined, such as the application route of the photosensitive dye, illumination, and stereotactic parameters.[158] Using noncoherent visible light instead of a laser beam also leads to ischemic brain damage, but at the same time, it reduces laser-mediated thermal tissue damage and the cost of the procedure.[159]

Based on its advantages of reproducibility, easy manipulation, minimal trauma, and flexible control of infarct size and location, the model is widely used in rats and mice.[160] Furthermore, there is still a lack of a suitable model for poststroke complications, and photothrombotic stroke in rats is supposed to be suitable for investigating the mechanisms of poststroke epileptogenesis.[161] Most importantly, it does not affect long-term survival. However, the biggest drawback of this model is the lack of a penumbra when cortical infarction is induced by direct irradiation of the skull, which is not consistent with clinical ischemic stroke.

3 | INTRACEREBRAL HEMORRHAGE

Compared with ischemic strokes, hemorrhagic strokes are less commonly occurred, but are more likely to be fatal. The mortality rate of hemorrhagic strokes (67.9%) was higher than that of ischemic strokes (57.4%). Hemorrhagic strokes include intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Accounting for approximately 10% of all strokes, ICH strokes are the most common hemorrhagic strokes.[162] Nontraumatic ICH strokes occur as a result of the spontaneous rupture of small vessels, leading to bleeding within the brain. Injury mechanisms in acute ICH include two processes, primary brain injury and second brain injury.[163] Mass effect and mechanical disruption of hematoma causes immediate primary brain injury due to increased intracranial pressure and mechanical compression of local structures.[163] Edema, inflammation, and clot toxicity are the major causes of secondary brain injury.[163] ICH triggers a series of pathophysiological processes, such as early hematoma enlargement, coagulation cascade activation and clot retraction, red blood cells lysis and infusion of hemoglobin, brain edema, necrosis and apoptosis, CBF reduction, and inflammation.[164] These complicated pathophysiological events lead to poor outcome and high mortality. The median case fatality of ICH is 40.4% in the first month and 54% in the first year—figures that have not declined over time.[165] Little progress has been made in the clinical treatment of ICH.[166] Thus, developing a preclinical model of ICH is quite important, which extends our understanding of the pathophysiology of ICH-induced brain injury and effectively promotes the speed of screening new therapeutic approaches. Two models are commonly used to mimic clinical ICH in rodents and large animals. One is the donor/autologous whole blood injection model. Another is a collagenase-induced hemorrhage model. Both models' strengths and weaknesses allow them to mimic only specific aspects within ICH pathophysiology.

3.1 | Whole blood injection model

In 1982, the blood injection model was first described by Ropper and Zervas, who promptly injected donor arterial blood into the caudate nucleus of rats to establish experimental ICH.[167] To produce ICH induced at arterial pressure in rats, the model was modified by connecting the cannula that was stereotactically inserted in the caudate nucleus or lateral ventricle to the femoral artery.[168,169] The main drawback of this approach is the uncontrollable hematoma size due to the fluctuation of blood pressure. Later, the model was further developed by Masuda et al, who stereotaxically injected 0.2 mL of autologous blood (drawn from a femoral vein) into the caudate nucleus.[170] To improve the reproducibility of the model, Yang et al, using a micropump connected to a stereotactic syringe, injected autologous femoral artery blood into the caudate nucleus constantly and slowly.[171] However, the above models inevitably reflux the blood along the needle track and uncontrollably extend the hematoma. A double blood injection method invented by Deinsberger et al in 1996 could solve this problem well.[172] First, a small volume of autologous blood is slowly injected into the caudate nucleus and then waiting for a few minutes to form a clot. Subsequently, the remaining blood is injected into the caudate nucleus again to produce a real hematoma.[172] Although double blood injection leads to the difficulty of second blood injection, it could minimize the possibility of blood reflux and significantly improve the reproducibility of the model. To date, the double blood injection model is widely used not only in rats but also in other animals, such as mice,[173,174] rabbits,[175] and pigs.[176] The whole blood injection model best mimics the hematoma mass effect and blood toxicity, but the model does not involve the rupturing of cerebral vessels. Thus, the blood injection model is not suitable for studying the bleeding mechanism and hemostasis treatment.

TABLE 3 The development of the generation of stroke models

Stroke models	Time	Authors	Approaches	Insult regions	Technical improvements
Ischemic stroke models					
Global ischemic stroke					
Incomplete global brain ischemia					
4-VO model	1979	Pulsi-Purkinjenelli and Brierley	Permanent occlusion of vertebral arteries and reversible occlusion of CCA	Forebrain ischemia	Vertebral artery was electro-cauterized at the second vertebra under microscope for highly reproducible forebrain ischemia model
2-VO model	1972	Eklof and Siesjo	Occlusion of bilateral carotid arteries alone or combined with reductions in the mean arterial blood pressure	Permanent BCAO could produce a model for chronic cerebral hypoperfusion-related neurodegenerative diseases Transient BCAO with a reduction in mean arterial blood pressure could establish a forebrain ischemic model	Modifying the time interval between the ligations of the BCA could ameliorate lethal effects BCAO alone could cause severe ischemic insults of the brain in SHRs
Complete global brain ischemia (CGBI)					
Aorta/vena cava occlusion model	1989	Hashimoto	Ascending aorta occlusion combined with bypass formation between the aorta and right atrium	Global brain ischemia	Using aortic and inferior vena cava occlusion balloons avoids surgical invasion of the thorax Aorta occlusion without vena cava occlusion is more suitable for short-term study on CGBI
Ventricular fibrillation (VF)	1981	Todd	Shocking the heart and urgent cardiopulmonary resuscitation	Global brain ischemia	
Chemical or gas hypoxia	2011	Yu, Xinge	Nitrogen gas hypoxia	Optic tectum	The addition of sodium sulfite is introduced for a chemical hypoxia
Focal ischemic stroke					
Transcranial occlusion	1981	Tamura	Occluding the stem of the proximal MCA through a small subtemporal craniectomy	The frontal cortex, the lateral part of the neostriatum, the sensorimotor and the auditory cortex in most animals	tandem occlusion of the distal MCA and ipsilateral CCA; combined occlusion of the MCA and bilateral CCA (3-VO models)

(Continues)

TABLE 3 (Continued)

Stroke models	Time	Authors	Approaches	Insult regions	Technical improvements
Endovascular filament middle cerebral artery occlusion (MCAo)	1985	Koizumi	Introducing a filament with a round tip from the ECA into the ICA and advancing it to block the origin of the MCA	One hour after occlusion, the ischemic cells are slightly scattered, whereas occlusion for more than 3 h causes severe ischemic lesions in the anterior neocortex and the lateral part of the caudate putamen supplied by the MCA After permanent MCA occlusion, irreversible injury appears first in the caudoputamen and then spreads to the cortex	Filaments coated with silicone, poly-L-lysine or paraffin reduce interanimal variability The diameter of the suture tip and the insertion distance of the suture affect reproductivity ECG, LDF and MRI can effectively guide filament placement
Embolic occlusion	1982	Kudo	Intracarotid injection of thromboembolus and artificial spheres	Parietotemporal cortex, hippocampus, thalamic striatum, and even a small proportion of the contralateral hemisphere	Utilizing microcatheter and LDF could ensure the occlusion of MCA more precise
Endothelin-1 occlusion	1995	Reid	Administrating ET-1 to the surgically exposed MCA	Caudate nucleus, the genu of the corpus callosum, and the cortex lying wholly within the territory of the MCA	Stereotaxic injection of ET-1 into the superficial cortex adjacent to the MCA can establish the similar infarct volumes Stereotactic injection of ET-1 into the cortex can be used to induce infarction in other specific brain regions, such as internal capsule ischemia and frontoparietal cortex infarction
Photothrombosis model	1985	Waston	Injecting photosensitive dye (rose bengal, erythrosin B) into circulation and then to irradiate the intact cranium of a specific area with a certain range of wavelength laser beams	Ipsilateral cortex	The laser beam can directly irradiate a certain vessel to produce cerebral ischemia in its supply regions. Photochemical MCA occlusion and reperfusion can be controlled by utilizing a 2-laser system Rose bengal plus thrombin aim to enhance the sensitivity to rt-PA treatment The application route of the photosensitive dye, illumination and stereotactic parameters is refined

(Continues)

TABLE 3 (Continued)

Stroke models	Time	Authors	Approaches	Insult regions	Technical improvements
Intracerebral hemorrhage					
Whole blood injection model	1982	Ropper and Zervas	Injecting donor/autologous arterial blood into the caudate nucleus	Caudate nucleus	injection of 0.2 mL of autologous blood into the caudate nucleus; micropump connected to a stereotactic syringe, injecting constantly and slowly; double blood injection method to prevent the blood reflux and hematoma expand
Collagenase model	1990	Rosenberg	Stereotactic injection of bacterial collagenase into brain regions	Specific cerebral parenchyma or intraventricular hemorrhage	Easy to control the size of the hematoma by adjusting the amount of collagenase

3.2 | Collagenase model

Collagenase is a metalloproteinase that degrades collagen IV in the basal lamina of the blood-brain barrier and eventually causes microvascular rupture and leakage surrounding the needle-puncture site. In 1990, the collagenase-induced ICH model was first described by Rosenberg et al.[177] The basic step of this model is stereotactic injection of bacterial collagenase into brain regions, leading to specific cerebral parenchyma or intraventricular hemorrhage.[177] The model best mimics bleeding, and the manipulation is easy. Furthermore, it is easy to control the size of the hematoma by adjusting the amount of collagenase. Thus, the model is commonly used in rodents and large animals.[178-181] However, this model is still unable to totally simulate the clinical incidence of ICH, especially in the following respects. Bleeding in the model is slow and diffuse due to rupture of small vessels and capillary beds around the injection site. In reality, ICH is mainly the result of the rupture of major brain vessels, and the bleeding caused by it is also very urgent, which is not consistent with the situation shown in this model. More importantly, bacterial collagenase exacerbates the inflammatory response, so it is not suitable for investigating the immune reaction of ICH.[182,183]

4 | CONCLUSION

At present, there are limited treatment strategies for both ischemic stroke and hemorrhagic stroke to improve the survival rate and prognosis of patients. These are undoubtedly due to the low translational rate of preclinical studies. To speed up the development of effective agents, the best research scheme should be determined according to the advantages and disadvantages of various animal models. Moreover, although the technologies of the models have been continuously generated in recent decades (Table 3), the current stroke models still need to be further improved. An excellent stroke model should have the following advantages: (1) simple to ensure that the repeatability of the model will not be affected by the technical difficulty; (2) suitable for a variety of small and large animals; (3) controllable harmful degree of stroke; (4) can simultaneously simulate common clinical complications, such as hypertension, diabetes, and hyperlipidemia; and (5) sensitive to the existing clinical treatment, for example, ischemic stroke models should be sensitive to rt-PA. In addition to constantly improving animal models to better mimic clinical onset, the research results based on different models need to be repeatedly verified by series of experiments. For example, after initial evaluations in young, healthy animals, further studies should be carried on aged animals with comorbidities such as hypertension. Furthermore, considering that the physiological functions of non-human primates and other large animals are more similar to those of human beings, we should gradually verify the therapeutic effect on these animals after verifying the treatment efficacy in various models of small animals.[11]

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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