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Prospects of Modeling Post-Stroke Epileptogenesis

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Abstract

This article describes the current status of post-stroke epilepsy (PSE) with an emphasis on post-stroke epileptogenesis modeling for testing new therapeutic agents. Stroke is a leading cause of epilepsy in an aging population. Late-onset “epileptic” seizures were reported in up to 30% cases after stroke. Nevertheless, the overall prevalence of PSE is 2–4%. Rodent models of stroke have contributed to our understanding of the relationship between seizures and the underlying ischemic damage to neurons. To understand whether acutely generated stroke events lead to a chronic phenotype more closely resembling PSE with recurrent seizures, a limited variety of approaches emerged in early 2000s. These limited methods of causing an occlusion in mice and rats show different infarct size and neurological deficits. The most employed procedure for inducing focal ischemia is the middle cerebral artery occlusion. This mimics the pathophysiology seen in humans, in terms of extent of damage to cortex and striatum. Photothrombosis and endothelin-1 models can similarly evoke episodes of ischemic stroke. These models are well suited to studying mechanisms and biomarkers of epileptogenesis or optimizing novel drug discoveries. However, modeling of PSE is tedious, highly variable, and lacks validity; therefore, is not widely implemented in epilepsy research. Moreover, the relevance of ischemic models to specific forms of human stroke remains unclear. Stroke modeling in young male rodents lacks clinical relevance to elderly population and especially women, due likely to sex differences. Nevertheless, owing to the neuronal damage and epileptogenic insult that these models trigger, they are helpful tools used to study acquired epilepsy and prophylactic drug therapy.

Graphical Abstract

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CONFLICT OF INTEREST STATEMENT

No author has a conflict of interest.

ROLE OF AUTHORS

All authors participated in the writing of this Review and collaborated with Dr. Reddy in creating data and concepts described in one or more portions of this paper.

Keywords

stroke; epilepsy; epileptogenesis; MCA; endothelin; post-stroke; seizures

INTRODUCTION

Epilepsy is a multitude of disorders that differ in their etiology and disease longevity. Primary epilepsy (50%) is idiopathic ('unknown cause'). In secondary epilepsy, or acquired epilepsy, (50%), seizures may result from a variety of conditions including stroke, trauma, tumors, encephalitis, and neurotoxicity (Engel et al., 2007; Reddy, 2013). The molecular mechanisms underlying the development of acquired epilepsy are not well understood. Epileptogenesis is a term used to describe the complex plastic changes in the brain that, after a precipitating event, convert a normal brain into a brain debilitated by recurrent seizures. Epileptogenesis is triggered by a diverse range of precipitating factors such as brain injury, stroke, infections, or prolonged seizures (Pitkanen et al., 2007; Reddy and Mohan, 2011). Etiologies of epilepsy fall under 3 categories: presumed symptomatic, idiopathic, and symptomatic. Presumed symptomatic epilepsies are generally symptomatic; however, the insults cannot be specified based on the present models (Engel, 2001). For idiopathic epilepsies, the etiology is unclear, but genetic factors seem to play a role. Symptomatic epilepsies fall in the category for which there is a specific insult in the brain that causes seizures. About 65 million people worldwide are affected by epilepsy (Delgado-Escueta and Porter, 1999). A greater portion of these patients have acquired epilepsy from a secondary cause such as a disease or brain injury from a stroke or cerebral ischemia (Luhdorf et al., 1986; Hauser, 1990; Hauser and Hesdorfer, 1990; Hauser et al., 1991; Hauser, 1992; Lambrakis CC and Lancman, 1998; Olsen, 2001; Myint et al., 2006).

Stroke is a leading cause of death and disability worldwide, and the majority of cases are ischemic stroke. Tissue plasminogen (tPA) is the only approved, life-saving treatment for ischemic stroke, which often limits neuronal injury. According to the American Stroke Association, in 2010, worldwide prevalence of stroke was 33 million, 16.9 million of those cases were first-time strokes. Stroke accounts for 11% of total deaths worldwide, making it the second-leading global cause of death behind heart disease. Stroke is also the leading cause of disability (Durukan and Tatlisumak, 2007; Durukan et al., 2008). Stroke is characterized as a focal neurological deficit that results from a disruption of blood flow and subsequent ischemia to a particular area of the brain. Irreversible damage to the brain

parenchyma occurs after five minutes of hypoxia. The most vulnerable areas of the brain are the hippocampus, cerebellum, neocortex and other areas in the ipsilateral hemisphere. There are two categories of strokes, hemorrhagic and ischemic. Hemorrhagic strokes occur when the vessels supplying brain parenchyma rupture and intracerebral bleeding ensues. Most common areas of intracerebral hemorrhage are the basal ganglia, which is supplied by the branches of middle cerebral artery (MCA). An ischemic stroke occurs when there is acute blockage of vessels, which leads to ischemia.

The three types of ischemic strokes include embolic, thrombotic, and hypoxic strokes. Embolic strokes occur when an embolus forms in another area of the body and travels to the cerebral vasculature to block a vessel. Thrombotic strokes occur when there is clot formation in a vessel typically over an atherosclerotic plaque. Lastly, hypoxic stroke is due to hypoxemia or hypoperfusion, which tends to affect watershed areas between two blood vessels. The overall mechanisms of stroke-induced neuronal injury are complex, including excitotoxicity, mitochondrial dysfunction, free radicals, protein misfolding, inflammatory changes, neural cell loss, injury or death of glia and astrocytes, and white matter injury (George and Steinberg, 2015). Neurological disability is a common early-onset attribute and is often followed by a long-term increase in risk of epilepsy in some patients.

As per the International League Against Epilepsy (ILAE), post-stroke epilepsy (PSE) is defined as two or more unprovoked epileptic seizures occurring at least 1 week after the stroke (Myint et al., 2006; Gibson et al., 2014). Post-stroke seizures can be early-onset or late-onset seizures. Early-onset seizures are classified as those occurring within the first week following stroke; late-onset seizures occur two weeks or later after stroke (Giroud et al., 1994; Lamy et al., 2003; Stefan and Theodore, 2012a; 2012b; Camilo and Goldstein, 2004). Early-onset seizures are caused by acute disruptions in metabolism and pathophysiology associated with stroke and are generally provoked (Kelly, 2002; 2007; Myint et al., 2006). Late-onset seizures are considered epileptic seizures because they are unprovoked and occur repeatedly. The initial stroke is followed by an epileptogenic phase that ultimately causes spontaneous seizures in 2 to 14% of ischemic stroke survivors (Kotila and Waltimo, 1992; Burn et al., 1997; Bladin et al., 2000; Dhanuka et al., 2001; Lossius et al., 2002; 2005; Lamy et al., 2003).

The actual prevalence of PSE is 2.3 to 43% (Meyer et al., 1971; Mohr et al., 1978; Forsgren et al., 1996; Jamrozik et al., 1999). This is partly due to a wide variability in the criteria used for stroke (ischemic or hemorrhagic), seizure occurrence, monitoring period, as well as the sex and age of the patient population (Kilpatrick et al., 1990; Kotila and Waltimo, 1992; Giroud et al., 1994; So et al., 1996; Burn et al., 1997; Camilo and Goldstein, 2004; Kammersgaard and Olsen, 2005; Benbir et al., 2006). In the elderly, cerebrovascular diseases account for more than half of the newly diagnosed cases of epilepsy (Mathern et al., 1995; 2002). Stroke severity and hemorrhagic stroke are the most predictive factors for developing PSE (Slapo et al., 2006). Overall, PSE generally occurs in at least 4 to 6% of the stroke population as evident from multiple clinical studies (Graham et al., 2013; Jungehulsing et al., 2013; Arntz et al., 2013). It appears that a substantial number of stroke survivors will develop epilepsy with increasing risk prior to 10 years after stroke.

This review is aimed to provide a brief overview of the experimental stroke models with an emphasis on advancing the ischemic models towards PSE modeling for the testing of new therapeutic agents. Currently, there are no specific drug therapies for preventing PSE in at-risk individuals. A greater understanding of PSE is required to facilitate the development of effective interventions for post-stroke epileptogenesis or disease-modifying therapies for PSE. The main emphasis is on late-onset “epileptic” seizures that define chronic epilepsy with spontaneous seizures. Late-onset epileptic seizures are defined as recurrent seizures occurring 1–4 weeks after the stroke. The early-onset seizures that commonly occur within 1 week due to the acute effects of the stroke are described elsewhere (Silverman et al., 2002; Slapo et al., 2006; Kelly, 2007).

EXPERIMENTAL STROKE MODELS

A multitude of stroke models in mice and rats have been created to mimic the disease that is experienced in stroke patients. In animals, stroke is modeled by a reversible or nonreversible blockage of cerebral vessels (Fig. 1A). Stroke severity or outcomes are typically assessed by neurological scores of sensory motor performance and histological analysis of the volume of infarction from postmortem specimens. The various methods of causing an occlusion in mice and rats show different infarct size and neurological deficits. An ideal stroke model should have desirable characteristics such as reproducibility, clinical significance, easy methodology, and limited collateral effects akin to human ischemia (Calloni, 2006).

In rodent models, cerebral ischemia consists of global and focal categories. Global ischemia leads to massive neuronal loss depending on the regions affected, duration of ischemia and time after stroke. Global cerebral ischemia is induced by a two-vessel occlusion and/or the four-vessel occlusion. Transient focal cerebral ischemia models, which mimic human acute ischemic stroke, enjoy widespread use including MCA occlusion (Harvey and Rasmussen, 1951; Hayakawa and Waltz, 1975; Coyle, 1982; Tyson et al., 1982; Yoshimine and Yanagihara, 1983; Longa et al., 1989), photothrombosis (Wester et al., 1992; Dietrich et al., 1993b; Markgraf et al., 1994; Schroeter et al., 2001) and endothelin-1 (ET-1) vasoconstriction models (Robinson et al., 1991; Sharkey et al., 1993; Sharkey and Butcher, 1995; Gartshore et al., 1997; Henshall et al., 1999). Nevertheless, the most employed procedure for inducing ischemia is the occlusion of the MCA via a thrombus. When motor behavior is tested, the animals that survive the ischemic event show deficits on the contralateral side of the ischemia. When these ischemic areas are studied histologically, MCA occlusions form small necrotic central regions and apoptotic peripheral regions (Fig. 1B) (Bliss et al., 2007; Caplan, 2007; Mendez-Otero et al., 2009; Balkaya et al., 2013).

In animals, neuronal lesion evaluation and quantification following stroke is an important aspect of acute outcomes. The infarct area after stroke models is usually determined by 2, 3, 5-triphenyl-tetrazolium chloride (TTC) staining at 1 to 5 d post-stroke (Fig. 1B). Infarct quantification is made by tracing the infarct zone of a high-contrast image of slices. It is important to ensure that the same ischemic and normal areas of the brain are available, the same relative slice is used for each brain, and only those brains that had infarcts extending throughout the thickness of the slice and into a consecutive slice are used for analysis. Therefore, infarct volume estimation is usually performed by the measurement of the

superior face of three to five sections in each animal. The area from the ischemic (ipsilateral) and non-ischemic (contralateral) hemispheres should be measured separately to express the infarct volume of ischemic hemisphere as a percentage of the non-ischemic hemisphere. In each case, the infarct area of two adjacent slices is averaged and then multiplied by the thickness of the slice, and values across all slices are added to obtain the volume of the infarct (Selvamani and Sohrabji 2010a b). TTC is a colorless dye that stains healthy brain tissue red when reduced by the mitochondrial enzyme succinyl dehydrogenase (Bederson et al., 1986). The absence of staining in necrotic tissue is then used to determine the area of a brain infarction. TTC staining is a postmortem standard in the experimental stroke field and serves as basic assessment tool for measuring infarct size.

There are other methods of quantification of the infarct area, such as cresyl violet (CV) staining. TTC and CV staining are routinely used methods to determine cerebral infarct volume and area. TTC and CV staining showed a high degree of correlation in infarct area and volume (Türeyen et al., 2004), indicating that both methods are suitable for producing accurate measurements of cerebral experimental infarcts. Immersion staining of unfixed brain slices with TTC is a popular method to determine cerebral infarction in preclinical studies; however, it is often difficult to apply immersion TTC-labeling to severely injured or soft newborn brains in rodents. A recent report shows the promise of an in vivo TTC perfusion-labeling method, which is based on an osmotic opening of blood-brain-barrier with mannitol-pretreatment (Sun et al., 2012). In addition, most silver stains are helpful to highlight the amount of degeneration in the ischemic sections. The sophisticated DWI/MRI or perfusion-weighted MRI is a good measure of the infarct size as a result of ischemic injury. The non-invasive MRI methods are very helpful in monitoring the progression of ischemic injury and repair.

MCA Occlusion Model

The most popular approach for inducing stroke is occlusion of the middle cerebral arteries (Rossmeisl et al., 2007). In these strokes, subcortical structures are damaged first, followed by the cortical structures. The most damaged structures are cortex and striatum. This mimics the pathophysiology seen in human striatocapsular infarcts, in terms of extent of damage and structures involved (Rossmeisl et al., 2007). These striatocapsular infarcts damage a great extent of the basal ganglia and the surrounding white matter tissue (Rossmeisl et al., 2007). Thromboembolic stroke is described earlier as an acute focal paradigm (Zhang et al., 1997a; b). One of the methods to induce MCA occlusion is by injecting a preformed fibrin clot into the internal carotid arteries. Due to the large size of the preformed fibrin clot this model is used with rats, most often unilaterally. Consequently, a pronounced ischemia is created in the territory supplied by the ipsilateral MCA. Since the vessels can naturally breakdown fibrin, this model provides a good timeline for fibrin clot breakdown and reperfusion (Wang et al., 2001a). At 3 hours after the fibrin clot injection all microvasculature supplying the cortex is reperfused but striatum deficits in perfusion are still present (Wang et al., 2001b). After 24 hours all microvasculature in the cortex and striatum are reperfused (Wang et al., 2001a). Using the preformed fibrin clot model, downstream branches are also occluded by the clot fragment (Heye et al., 1992; Overgaard et al., 1994; Busch et al., 1998; Wang et al., 2001b).

Fibrin microemboli can be used to induce stroke in mice. This model varies from other embolic models in a multitude of ways. Since these microemboli are much smaller (2.5 – 3 μm) than previous clots (200 μm to millimeters) they are able to reach the microcirculation (Atochin et al., 2004). One way this model differs from other embolic models is that one can vary the dose of the fibrin microemboli, which directly influences the extent of the cerebral damage (Murciano et al., 2002; Atochin et al., 2004). With a moderate dose of the fibrin microemboli a reproducible and momentary reduction in cerebral blood flow is seen (Atochin et al., 2004). However, blood flow is reestablished naturally reflecting physiological fibrinolysis (Atochin et al., 2004). A combination of transient MCA occlusion and common carotid artery is another model to produce consistent cortical infarcts with little damage to subcortical structures and hippocampus (Aronowski et al., 1997; Kelly et al., 2006). This model is designed to simulate the aspects of human strokes.

MCA Occlusion by Filament

The reversible MCA occlusion model has been studied greatly because of its similarity in recanalization of a thrombosed or embolized vessel by t-PA (Longa et al., 1989; Garcia et al., 1993; Chiang et al., 2011; Bake et al., 2014). In this model, the MCA is occluded using a filament suture that is accelerated along the internal carotid artery through the external carotid artery until it reaches the MCA in the skull (Fig. 1A). Once the suture is 10 mm past the bifurcation point of the common carotid, the suture is tied off and held in place for a varying amount of time and then removed to allow reperfusion to occur (Chiang et al., 2011). This model allows a less invasive and simpler approach to occlude a cerebral vessel compared to the craniotomy models (Liu et al., 2009a). This model is typically used in rats but with advanced surgical skill, can be performed in mice as well. Mice have been used sparingly as experimental models because, unlike rat models, mouse MCA occlusion is technically more challenging and unreliable due to high mortality, lack of functional behavior tests, and the need for tedious blood flow monitoring. This model has been used to learn more about ischemic stroke for many years; however, the development of infarction within the territory supplied by the MCA is not well understood (Liu and McCullough, 2011). Thus there are variances in infarct size due to disagreements over the proper time to measure the impact of therapeutic agents (DeVries et al., 2001; Culmsee et al., 2005; Hoyte et al., 2006).

Patients that are older have an increased mortality rate as well as more functional deficits following an ischemic incident (Rojas et al., 2007). Even though it would be more clinically relevant to perform MCA occlusions on aged rats and mice, there are limited studies that have used older animals. As animals age there are several physiological and chemical changes that arise (Anyanwu, 2007; Li et al., 2007, McCullough et al., 2005). In general it is more challenging to complete MCA occlusions on older rodents. As they age they become heavier, accumulate greater levels of visceral fat, and have higher mortality post occlusions (Liu et al., 2009b). Aged animals also have more rigid vessels, causing the insertion and the acceleration of the filament to become more challenging. (Liu and McCullough, 2011). Therefore, one of the drawbacks to the MCA occlusion model is its lack of application to older animals, which would be more clinically applicable (Liu and McCullough, 2011).

Over the past 20 years the intraluminal filament stroke model has been employed extensively (Yamashita et al., 1997; Li et al., 1999; Reglodi et al., 2000; Yanamoto et al., 2001; Gerriets et al., 2003). The majority of human strokes are smaller in size from 28 to 80 cm³ (Saver et al., 1999; Carmichael, 2005). The percentage of infarcted tissue in relation to the total volume of the ipsilateral hemispheric volume is from 5 to 14% (Lyden et al., 1994). In malignant human brain infarctions, which make up 10% of human stroke cases, this percentage is higher, approximately 39 to 47% (Foerch et al., 2004; Oppenheim et al., 2000). The majority of recent publications that use a mouse MCA occlusion model report an infarct volume affecting 21 to 45% of the ipsilateral hemisphere (Belayev et al., 1999; Boutin et al., 2001; McColl et al., 2004). The bulk of experimental MCA occlusion models appear optimized for greater infarct outcomes than human stroke. Thus, most of the mouse MCA occlusion models do not resemble the typical case of human stroke, but instead they resemble more closely a malignant human brain infarction (Carmichael, 2005).

Cortical Photothrombosis

Photocoagulation of the common carotid artery is another method used to induce perfusion deficits in the MCA. This technique is used more in mice; however, it can also be performed in rats. There are two distinct techniques of photothrombosis: cortical photothrombosis and direct photothrombosis of the internal carotid artery. The process behind the cortical thrombosis model requires a laser-driven photochemical technique, which results in direct peroxidation of the endothelial membrane, due to single molecular oxygen (Lozano et al., 2007). The technique is generated by the photosensitive dye, Rose Bengal (Rosenblum and El-Sabban, 1977; Watson et al., 1985). Rose Bengal is injected into the animal intraperitoneally or intravenously and activated by an external light source that penetrates the translucent skull. Oxygen is the only photoproduct when rose Bengal or erythrosine B is incorporated as the characteristic Type II photosensitizing dye (Watson et al., 1987; 2002). The photochemically induced endothelial damage selectively attracts platelets, which then degranulate and start a process of aggregation (Lozano et al., 2007). This results in a bulky but non-obstructive platelet thrombus inside the ipsilateral common carotid artery. The thrombus delivers a regular stream of emboli, which creates multiple downstream embolic infarcts (Dietrich et al., 1993a, b). Photochemically induced thrombus models require an intact hemostatic system, which interact with the arterial endothelium, thus making it thrombogenic by photochemical reaction (Lozano et al., 2007).

Although the photothrombotic model resembles some aspects of the human stroke, there are issues with occlusion reproducibility and consistency (Dietrich et al., 1988; Joseph et al., 1991; Lozano et al., 2007). As is seen in human patients with atherosclerotic disease that have varying sizes of infarcts in different locations, rodents that experience non-occlusive arterial injury may not have ischemic injuries in the same territories or even the same extent of cerebral damage (Lozano et al., 2007). Furthermore, vascular anatomy along the embolus path deviates among individuals and species; these small changes in blood flow, and recanalization time could possibly vary the size and territory of embolic infarcts (Liebeskind, 2005; Valeri et al., 1987; Faraday and Rosenfeld, 1998; Dietrich et al., 1987; Johnston et al., 1994; Wolberg et al., 2004). In terms of clinical relevance, the

photocoagulation of the internal carotid artery is applicable towards the thromboembolic stroke populations, accounting for 75% of cerebral vessel occlusions (Lozano et al., 2007).

Endothelin-1 Vasoconstriction

Focal ischemic lesions can also be induced by stereotaxic injections of endothelin-1 (ET-1) in the gray or white matter. ET-1, isolated from aortic endothelial cells, is a peptide that has a strong and long-lasting vasoconstrictive effect in various vascular beds (Yanagisawa et al., 1988; Rubanyi and Polokoff, 1994). In the brain, ET-1 acts on a multitude of ET receptors that are present throughout the CNS on the vascular endothelium and also present on astrocytes (Venance et al., 1998), microglia (McLarnon et al., 1999), and neurons (Rubanyi and Polokoff, 1994). Endothelin type A receptors in the rat CNS are located on smooth muscle cells of pial arteries of the cerebral cortex. Endothelin acts on arteries as a potent vasoconstrictor. For instance, high doses of ET-1 directly injected into the brain parenchyma of rats have shown to reduce striatal blood flow by 60% in 20 min while leaving systemic blood flow unaffected (Fuxe et al., 1992). In addition, topical administration of ET-1 directly on the MCA has been shown to decrease cerebral blood flow in rats and cats (Mima et al., 1989; Robinson et al., 1991).

The stereotaxic injection of ET-1 for MCAO is typically done in rats and not mice since mice lack the ET-1 receptor and therefore injection would produce little to no decrease in cerebral blood flow. ET-1, when injected in white or gray matter, typically reduces cerebral blood flow within an hour after the injection (Hughes et al., 2003). This decreased cerebral blood flow typically lasts up to 7 hours or more, depending on the dose and site of infusion (Hughes et al., 2003). When cerebral blood flow is altered, effects from other insults besides ischemia can come into play. Usually when cerebral blood flow is reduced, the blood-brain barrier (BBB) can be compromised; the amount of damage to the BBB depends on the duration and extent of the reduction of blood flow (Hallenbeck and Dutka, 1990). When ET-1 is directly injected on to the striatum, no breakdown of the BBB is seen. This is a beneficial component of this model since it will not be confounded by the involvement of vasogenic edema to lesion formation (Hughes et al., 2003). However, cell loss is still observed and contributes to cytotoxic edema due to the decreased cerebral blood flow (Hughes et al., 2003). There are minimal exogenous effects to the animal in this model since the BBB is not destroyed. This model serves as a good method to understand the mechanisms behind ischemia induced cytotoxic edema in the gray and white matter areas. It is also beneficial to analyze the clinical potential of novel treatments that preserve axonal integrity.

Sodium Laurate Injection

Sodium laurate injected directly into the carotid artery can also model stroke in animals, and is typically used in rats. Arterial injection of sodium laurate is known to cause tissue necrosis in the downstream arteries, leading to platelet aggregation, platelet adhesion, and lastly to an obstructive thrombus (Kumada et al., 1980). When injected into the internal carotid artery, sodium laurate causes lacunar infarcts, which are downstream infarcts resulting from the obstruction of the perforating branches of the major cerebral vasculature (Fisher, 1982; Kappelle and Gijn, 1986; Toshima et al., 2000). This model presents several

significant advantages over other models. The main arteries occluded via endothelial injury and consequential thrombus formation are the perforating arteries, which allows researchers to study lacunar infarcts properly (Toshima et al., 2000). Additionally, minor cerebral infarcts due to microthrombotic obstructions, in combination with neurological abnormalities, can be induced (Toshima et al., 2000). Specifically, this model leads to small arterial wall injuries via microthrombi, thus providing an excellent platform for learning more about the treatment and pathophysiology of minor cerebral infarcts (Toshima et al., 2000).

Spontaneous Stroke Model

Another stroke model that is often used in experimental interventions is the spontaneous stroke model. In this model, spontaneously hypertensive stroke-prone rats are used, which naturally develop a multifaceted type of cerebrovascular pathology (Okamoto et al., 1974; Volpe et al., 1998). For this specific rat strain, brain vascular disease is induced by a hypertensive state and is magnified by the introduction of a low-protein, low-potassium, and high sodium diet, also referred to as the Japanese permissive diet (Yamori et al., 1984; Sironi et al., 2001; 2003; 2004). Moreover, it has also been reported that when compared to other surgical stroke models such as MCA occlusions, brain damage in the spontaneous stroke model, results from the breakdown of the BBB in the absence of cytotoxic edema (Huber et al., 2001; Guerrini et al., 2002). It is known that in several inflammatory conditions, the BBB is broken down (Abbot, 2000; Huber et al., 2001). Thus, brain injury is possibly triggered by the extravasation of blood-borne cells that have greater BBB penetrability (Couraud, 1998; Gigante et al., 2003). This strain of rats has alterations in their vessel walls that explain the reason for BBB breakdown. In terms of clinical relevance, many neurological disorders with strong inflammatory mechanisms such as stroke, Alzheimer's disease, and multiple sclerosis have been shown to include changes in concentration and composition of CSF proteins along with BBB integrity (Couraud, 1998; Kappos et al., 1999; Abbott, 2000; Berzin et al., 2000; Davidsson et al., 2001).

POST-STROKE EPILEPTOGENESIS

There are some strong predictors for post-stroke epileptogenesis. Stroke severity and hemorrhagic stroke appear to be the two most consistent factors (Slapo et al., 2006; Kelly, 2007; Olsen, 2001). According to the Oxfordshire community stroke project, 11.5 % of patients with stroke are at risk of developing post-stroke seizures within five years (Burn et al., 1997). Another study was conducted where Hauser and colleagues analyzed the incidence of all unprovoked seizures and epilepsy in Rochester, Minnesota during the years of 1935 through 1984. From all the cases analyzed, they found that cerebrovascular disease was a factor in 11% (Hauser et al., 1993). The increased incidence of PSE has been well documented; there is a strong need for therapeutic treatments specific to this condition. Although predicting who will have seizures after a stroke is challenging, there are some risk factors correlated with a greater frequency of post-stroke seizures such as stroke severity, cortical damage, the degree of ongoing disability after a stroke, hippocampus involvement, the primary neurological deficit, and the involvement of several territories of the brain (Browne and Holmes, 2001). In cases of subarachnoid hemorrhages, the likelihood of post-

stroke seizures is influenced by EEG abnormalities, structural brain lesions, and partial epileptic seizures. Despite growing awareness about stroke as a major cause of epilepsy, especially in the aged population, research is limited towards identifying a clinically-relevant model, which is essential to understanding the post-stroke epileptogenesis. A limited array of models such as MCA occlusion and photothrombosis are facilitating post-stroke modeling in animals (Kelly, 2007).

Mechanistic Insights of PSE

Mechanisms of PSE and its risk factors are poorly studied, mainly due to limited developments in animal modeling of PSE. Generally, post-stroke epilepsies occur in three stages (Fig. 2). The first stage is the original brain insult due to stroke, the second stage is the latent period where although no seizures occur, molecular and cellular changes in the brain are occurring, and the third stage is the presence of recurring seizures (Pitkanen et al., 2007; Reddy, 2013). The development of epileptogenesis is thought to be a step-function of time after the brain injury, with a latent period present between the brain injury and the first unprovoked seizure. Various studies report that during epileptogenesis, a vast degree of cellular changes occur—for example, gliosis, cell death, neurogenesis, axonal, and dendritic plasticity, angiogenesis, and rearrangement of extracellular matrix (Jutila et al., 2002). These changes typically occur in the latent period after an initial brain insult. Thus, the latent period represent a critical window for effective “antiepileptogenic” interventions for preventing epilepsy in people at risk.

The pathophysiology of PSE is complex and multifaceted (Fig. 3). Stroke is a common epileptogenic injury in the elderly. The main predictors for the development of PSE are stroke severity, cortical stroke and hemorrhagic stroke (Slapo et al., 2006). Based on the age and predictive factors, the potential mechanisms underlying the PSE include: (i) loss of neurovascular unit integrity; (ii) hypoxia and metabolic dysfunction; (iii) blood-brain barrier dysfunction; and (iv) glutamate excitotoxicity (Sun et al., 2001; 2002; Kessler et al., 2002; Silverman et al., 2002; Myint et al., 2006). The disordered cerebral metabolism and perfusion leading to chronic neuronal injury and inflammation can trigger the progressive epileptogenic changes (Fig. 3). Neuronal injury or neurodegeneration at the infarction sites or surrounding areas including the penumbra can activate the progressive epileptogenic process including excitatory neuron axonal sprouting. Numerous individual studies have been performed in order to better understand the mechanisms behind these various possibilities. Analysis of the characteristics of cortical damage shows that extensive lesions with cortical involvement tend to be more frequent in patients with PSE (Gupta et al., 1988; Ryglewicz et al., 1990). Complex changes in neuronal excitability and gliotic scarring are most probably the primary cause of post-stroke epileptic seizures (Myint et al., 2006). Such common epileptogenic pathways are supported by the clinical studies that show PSE occurs in patients with ischemic and hemorrhagic strokes. Furthermore, sustained inflammation due to secondary triggering factors from stroke plays a critical role in epileptogenesis.

A cascade of devastating acute injuries contributes to seizures after stroke. The function of the BBB, or neurovascular unit which regulates the passage of blood constituents to brain parenchyma, is compromised by stroke and reperfusion. The neurovascular unit is comprised

of the microvascular endothelium and neuronal and glial cell elements (astrocytes) in close proximity. The most consistent and well-characterized risk factor for seizures in both cerebral infarction and hemorrhage is cortical involvement (So et al., 1996; Arboix et al., 1997; Burn et al., 1997; Beghi et al., 2011). Cortical infarcts can cause a 2-fold increase in risk of seizure after stroke; cortical hemorrhage had an almost 3-fold increase in risk (Bladin et al., 2000). Hemorrhagic stroke was a significant risk factor of seizures as compared to ischemic stroke. Patients with late-onset seizures were at greater risk of epilepsy as compared to those with early-onset seizures (Bladin et al., 2000; Bladin and Bornstein, 2009). Stroke severity is one of the most supported risk factors in the PSE population. It is consistent with multicenter studies that link more damaging strokes to a higher risk of developing PSE (So et al., 1996; Arboix et al., 1997; Burn et al., 1997; Bladin et al., 2000). Accordingly, in the cerebral infarction, larger strokes or multiple lesions, severity of the disability or neurological deficit, and hippocampal involvement are associated with a higher risk of post-stroke seizures (Lancman et al., 1993; So et al., 1996; Bladin et al., 2000; Browne and Holmes, 2001). Additional factors such as gender, age, and disease states can also affect the risk and prognosis of PSE (Gibson, 2013; Sohrabji et al., 2015).

Experimental Aspects of PSE and Outcome Analysis

Experimental aspects of PSE are very similar to chronic epilepsy models, like traumatic brain injury (TBI) or post-SE epileptogenesis (Pitkänen et al., 2007; Losher and Brandt, 2010). The stroke induction serves as the initial precipitating injury, akin to mild to moderate TBI. After stroke, animals are monitored for electrographic and behavioral seizures or seizure-like activity for several weeks or months. The primary outcome measurements include: (i) the latent period to first (late-onset) spontaneous seizure; (ii) incidence of animals with spontaneous recurrent seizures; (iii) frequency of spontaneous seizures; and (iv) severity and duration of spontaneous seizures. The surrogate measurements include preictal and interictal spikes, ripples, and seizure threshold. The secondary parameters include: (a) behavioral alterations (learning and memory and others behavioral tasks); and (b) neuropathology of brain sections (neurodegeneration, neuronal sprouting, and neurogenesis).

Electrophysiological events play a key role in the progression of brain injury from regions of primary ischemic or traumatic insult to adjacent regions of secondary injury. EEG seizure activity can occur in the absence of overt clinical manifestations of stroke-induced seizures. Indeed, it is evident that distinct episodes of generalized seizure discharges occur in a high proportion of MCAo-injured animals, but without overt manifestations or disturbance of normal motor behavior. Therefore, continuous EEG monitoring is a critical component of the overall experimental design for PSE. Various video-EEG montages are used to acquire EEG signals depending on the model and study design. EEG recording electrodes are implanted immediately after stroke induction or a few days after ischemic injury. Video recordings are very helpful to monitor behavioral seizures and the overall activity of the post-stroke animals. There are two phases of post-stroke monitoring for seizure activity: acute phase and chronic phase monitoring. In the acute phase monitoring, animals are returned to recording chambers immediately after ischemic procedure and continuous EEG recordings are taken for up to 72 h or more. Animals are observed carefully for signs of

tonic/clonic motor convulsions and other abnormal behaviors. Epileptiform discharges serve as indicators of hyperexcitability or synchronous seizure activity. Behavioral manifestations of seizures are scored by the Racine scale of 0 to 5 (Racine, 1972). Electrographically, seizure activity can be detected by both the ipsilateral and contralateral cortical electrodes. Focal discharges are often evident from the ipsilateral electrode.

During the chronic phase, continuous EEG recording is made for the full duration of the study, from 1 to 12 months after stroke. Apart from EEG, concurrent behavioral monitoring is critical to discern the artifacts of electrographic events and also to compare the EEG and behavior or motor seizure activity. Continuous long-term monitoring of seizure activity is achieved by commercially available wireless video-EEG systems or custom-made tethered systems. Development of spontaneous seizures is most accurately identified by continuous video-EEG recordings 4 to 12 months following stroke in rats. Intermittent recordings at 1, 3, 6 and 12 months is not ideal due to the unpredictable nature of seizure occurrence that can be missed. Such intermittent monitoring may lead to false negative outcomes. The identification of a spontaneous seizure is generally determined based on the analysis of the EEG files. EEG activity that differed from the background (2-fold or more) with a clear onset and offset is defined as an EEG seizure. A typical spontaneous seizure will last from 20 to 50 s in duration with a high-amplitude, high-frequency rhythmicity. An electrographic seizure is defined as epileptiform discharge or paroxysmal discharge with rhythmic repetitive waveforms that lasted for at least 5 s, had a clear beginning and ending, and temporal evolution in amplitude and frequency. If an electrographic seizure occurred, the severity of the behavioral seizure is scored based on the video image by an independent observer or automated software. Number, duration(s), and frequency of seizures during the monitoring period will serve as primary indicators of epileptogenesis. PSE modeling is interpreted as positive if there is an enduring alteration in the brain (stroke) or predisposition to seizures with at least two spontaneous seizures. Finally, the extent of neurodegeneration and aberrant axonal sprouting are assessed by histological analysis. In many PSE models, there is mossy fiber sprouting to the inner molecular layer of the dentate gyrus, even though the density can vary between models or duration of monitoring period.

Analysis of previous reports will lead to answers to critical questions such as: Do animals develop spontaneous seizures after transient ischemia? How should epileptic seizures (onset time, incidence, seizure types and behavioral correlates) in animal models of stroke be defined? What are critical approaches and designs for detecting epileptogenesis and spontaneous seizures? Are epileptogenic abnormalities linked to axonal plasticity in the hippocampus? Is there a temporal correlation between extent of injury and late-onset seizures? What are experimental complications or variables to be considered in aged animals? Answers to these and many other questions will facilitate the identification of molecular targets for antiepileptogenic treatments, the design of treatment paradigms, and the relevancy of current models to human epilepsy.

Experimental PSE Models

A limited variety of experimental stroke models have been utilized to check for epileptic seizures by EEG recording or behavioral monitoring. Early onset seizures were apparent in a

majority of stroke models such as MCA occlusion (Kudo et al., 1982; Lu et al., 2001; Wang et al., 2001a, b; Hartings et al., 2003; Williams et al., 2004). These seizures are due mostly to an ischemia-induced response rather than true epileptic events. A detailed mechanistic description of such early-onset seizures is beyond the scope of this article. The field of PSE is still in its infancy due to many challenges in successful PSE modeling. There are very limited reports of long-term follow-up for detecting recurrent epileptic seizures (Pitkanen et al., 2007). The general features of selected PSE models are outlined in Table 1 and the chronic PSE animal studies are summarized in Table 2

PSE modeling is mostly implemented in young male rodents. This is another major issue for lack of clinical relevance to aged population, especially to women due to potential gender differences in stroke outcomes. Age and sex differences are much more prevalent in stroke and also are widely recognized in rodent models (Bake et al., 2014; Giorgi et al., 2014; Koppel and Harden, 2014; Sohrabji et al., 2015). Stroke studies have shown that young females have a smaller infarct and better cerebral blood flow than age-matched males (Alkayed et al., 1998). Young females sustain a smaller infarct compared with young males or aged female mice (Liu et al., 2009); however, aging reverses these sex differences, such that aged females showed significantly more mortality and poorer stroke outcomes compared with older males (Manwani et al., 2011). Sex differences have also been noted at middle age, where adult female rats have smaller infarcts than middle-aged females (Selvamani and Sohrabji, 2010). Therefore, selection of a battery of models in both genders and aged rodents is important to get clinically-relevant insight from the PSE modeling.

MCA Occlusion PSE Model

The MCA is the most commonly affected vessel in stroke (Mohr et al., 1986) and its occlusion is associated with late-onset seizures and epilepsy (De Carolis et al., 1984; Saguegna et al., 1984). The MCA occlusion model of stroke has been utilized to investigate whether the initial ischemic injury is followed by an epileptogenesis phase and eventually by recurrent spontaneous seizures in rats (Pitkanen et al., 2005; Karhunen et al., 2003; Karhunen et al., 2006; Kelly et al., 2006; Miller et al., 2013). Although stroke as an injury factor for epilepsy is widely recognized, the experimental PSE modeling is highly disappointing with little or no evidence of post-stroke epileptic seizures. It was found that combined occlusion of the MCA and CCA does not induce epilepsy in rats during a 6-month follow-up (Kelly et al., 2006). Similar findings were obtained with the intraluminal filament model of MCA occlusion followed by 10 months of video-EEG monitoring (Karhunen et al., 2003). However, animals had a long-lasting sensorimotor deficit and spatial memory impairment. It is unclear whether MCA stroke is associated with progressive change in seizure threshold and epileptiform-like activity, which are indices of subclinical epileptogenic process.

To create a better PSE model, the MCA occlusion has been implemented in an age-dependent fashion using young adult (4 months old), middle-aged (12 months old), and aged (20 months old) rats (Miller et al., 2013). By utilizing permanent and transient (3 h) unilateral MCA and common carotid artery (CCA) occlusion coupled with long-term video-EEG monitoring, these authors have assessed EEG and behavioral seizures associated with

post-stroke epileptogenesis. About 14% animals demonstrated seizure activity after MCA/CCA occlusion, including middle-aged and adult animals. The latency for first spontaneous seizure was 316 days. However, there was no evidence of mossy fiber sprouting in the Timm staining of these animals, indicating that the hippocampus may not be affected by MCA/CCA stroke. Mossy fiber sprouting is a hallmark morphological feature of limbic epileptogenesis in rodent epilepsy models (Rao et al., 2006; Reddy and Kuruba, 2013).

Rat models of MCA occlusion are the standard models to induce cerebral ischemia and infarction. In rats, distal MCA occlusion does not produce consistent infarction due to vascular anatomy. The hippocampus can lie within the region of ischemic injury because it is perfused by the PCA that can be blocked by MCA occlusion (Del Zoppo, 1998). In contrast, the hippocampus is generally unaffected by the MCA occlusion because of differences in vascularity (Kelly, 2007). Although hippocampus is not the primary site of ischemic injury with MCA occlusion, a long-term neurodegeneration is evident within this region from such an injury. Nevertheless, the overall relevance of MCA occlusion model to PSE modeling is uncertain.

ET-1 PSE Model

In another PSE model, the ET-1 stroke paradigm was utilized to check for post-stroke epileptic seizures (Karhunen et al., 2006). MCA occlusion was induced by intracerebral injection of ET-1 (120 pmol) and rats were followed-up for 6 or 12 months. Intermittent video-EEG recordings indicated late seizures in one of eight rats during 6 months of video-EEG recordings and in zero of 18 rats during 12 months of video-EEG recordings (Karhunen et al., 2006). However, epileptiform interictal spiking was observed in 35% of animals (N=26). There was no evidence of mossy fiber sprouting. Morris water-maze test revealed no apparent differences in memory function. Thus, production of MCA stroke by intracerebral ET-1 injection appears a weak trigger of epileptogenesis in adult rats. It remains unclear if these animals displayed any hyper-susceptibility to chemoconvulsants or decreased seizure thresholds, which may reflect their hyperexcitability status. Since a higher dose of ET-1 can cause a greater infarction, it is likely that a high-dose regimen might lead to a positive PSE occurrence.

Recently, we studied the long-term epileptic seizures in young and aged female rats after stroke induced by MCA occlusion (Park et al., 2016). MCA Occlusion was induced by intracerebral injection of endothelin-1 (600 pmol) in adult (6 months, cyclic) and middle-aged (11 months, acyclic) female rats. Animals were recorded for the occurrence of behavioral and electrographic spontaneous seizures by a continuous 24/7 video-EEG system for one week at 2, 4, 6, 8, 10, and 12 months. Epileptiform “seizure-like” discharge were detected in 25% (1 of 6 adults) and 40% (2 of 5 middle-aged) of rats at 4 months; and 50% (1 of 2 adult) and 33% (1 of 3 middle-aged) at 6 months after stroke; spontaneous seizures were not evident at 8, 10, or 12 months after stroke (Park et al., 2016). Overall, these results indicate that MCAO-induced stroke is a potential epileptogenic trigger with extremely low incidence, but this condition may be sensitive to a subsequent hit or secondary brain injury.

Photothrombosis PSE Model

Cortical photothrombosis model has been utilized to check for the development of epileptogenesis and memory deficits (Kelly et al., 2001; Liu et al., 2002; Kharlamov et al., 2003; 2007; Karhunen et al., 2007). There was some evidence of epileptogenesis after cortical photothrombotic lesion in rats. In contrast to MCA occlusion models, a model of small cortical photothrombotic lesions with Rose Bengal dye induces epilepsy in up to 50% of the animals (Kelly et al., 2001; Kharlamov et al., 2003). These studies show that PSE can be induced in rats using cortical photothrombosis. A recent study has confirmed these findings (Karhunen et al., 2007). In this study, spontaneous seizures were recorded by intermittent video-EEG monitoring at 2, 4, 6, 8, and 10 months for 7–14 days (24 h/day). Epileptic seizures were detected in 18% of rats that received photothrombosis. The average seizure frequency was 0.39 seizures per recording day and mean seizure duration was 117 s. Spatial learning and memory assessment in rats with photothrombotic lesions shows evidence of cognitive impairment. Development of epilepsy was accompanied by light mossy fiber sprouting in the inner molecular layer of the dentate gyrus, indicating that the hippocampus might be affected by PSE. These findings suggest that photothrombotic stroke in rats is a viable animal model for investigating the mechanisms of post-stroke epileptogenesis.

CLINICAL PROSPECTS

Although epileptic seizures are a well-known complication of stroke, there is limited data regarding the long-term rate of seizures in patients who have a stroke. Recently, Merkler and colleagues have analyzed the long-term risk of seizures following stroke to reaffirm the likelihood of developing seizures after suffering a stroke (Merkler et al., 2016). They examined hospital visits from 2005–2013 in California, Florida, and New York. They identified over 600,000 patients with stroke and found that 15% of stroke patients had a seizure an average of three years after follow-up. Patients who have hemorrhagic stroke may face an even higher rate of seizures.

The primary therapeutic interventions for PSE remain antiepileptic drugs (Hauser, 1992; Brodie et al., 1999; Reddy, 2014). The recommended first line antiepileptic treatments are sodium valproate, topiramate, lamotrigine, and carbamazepine. A recent population-based study demonstrates that valproic acid treatment to late-onset post-stroke epilepsy patients show better seizure control than phenytoin (Huang et al., 2015). Other monotherapies include phenobarbital and clonazepam along with phenytoin, which is used as an alternative in older patients. With these drug treatments the main limitation to their use is drug associated sedation. For older patients treatment has to be monitored more closely due to hepatic enzyme induction by antiepileptic drugs, which can lead to drug interactions (Myint et al., 2006; Reddy, 2010). Additionally, the effects of aging on drug clearance could lead to higher levels of toxic effects.

Seizure prophylactic treatment is advised by the Stroke Council of American Heart Association for acute cases of subarachnoid and intracerebral hemorrhages (Broderick et al., 1999). Some of these patients that have deep cerebellar or subcortical lesions have a lower chance of developing recurrent seizures and do not need regular prophylactic treatment. On

the contrary, patients that elicit seizure incidents greater than two weeks post-stroke have an increased chance to develop recurrent seizures and should be placed on regular prophylactic treatment. Furthermore, seizures that start early need to be therapeutically treated for a month and if during the treatment seizure activity is absent the medicine can be stopped (Qureshi et al., 2001). In terms of daily living the proper precautions that are taken with epileptic patients are also taken with patients that have PSE or post-stroke seizures. For example, routine follow up visits to determine drug side effects, step wise increment of dose regimen to maintenance dose, supervision of activities such as cooking, exercising, and swimming (Kotila and Wiltimo, 1992; Kalpatrick et al., 1990; Myint et al., 2006). When diagnosing these patients it is imperative that alternative differential diagnoses be considered because the outward cause of the seizures, for example, stroke could be disguising the real cause of the seizures such as metabolic, neurological, and cardio-vascular issues (Suman and Das, 2003; Myint et al., 2006).

CONCLUSIONS AND FUTURE DIRECTIONS

Stroke is a major cause of epilepsy and a substantial proportion of patients with stroke develop PSE, particularly among the elderly. The long-term risk of seizure after stroke appears temporally similar to that after TBI, which is widely recognized as a strong long-term seizure risk factor. The prevalence of PSE varies between 3.3 and 13%, depending on factors like onset of the studies and duration of the follow-up. There are two predictive factors for developing PSE --stroke severity and hemorrhagic stroke among other related factors. The pathophysiology of PSE is complex and multifaceted, most likely involving chronic neuronal injury and inflammation. Like symptomatic epilepsy, PSE is treated successfully with standard antiepileptic drugs. However, there is no approved therapy for preventing PSE. There is an unmet need for drugs that truly prevent the development of PSE ('antiepileptogenic agents') or alter its natural course to delay the appearance or severity of epileptic seizures ('disease-modifying agents') in people at risk for epilepsy. Understanding the causes of the epilepsies and prevention of epilepsy and its progression are identified as top priorities in the 2014 National Institutes of Health NINDS Benchmarks for Epilepsy Research. A clinically-relevant, valid approach to post-stroke modeling is essential for advancing the goal of preventing epilepsy in people with a stroke history. A key problem in understanding the PSE is that very little is known about post-stroke epileptogenesis in animal models. A limited array of stroke modeling, including MCA occlusion, photothrombosis and ET-1 paradigm, is facilitating PSE modeling in animals. Kelly and collaborators (Kelly, 2002; 2006; 2007; Kelly et al., 2001; 2006) and other workers such as Pitkänen and co-workers (Pitkanen, 2005, 2007; Karhunen et al., 2003; 2006; 2007) have made apparent contributions to post-stroke epileptogenesis.

Epidemiologic data indicate that TBI and stroke as a cause of epileptogenesis in adults and elderly. Unlike TBI that triggers epilepsy in up to 53% of patients, stroke accounts for epilepsy development in up to 15% of patients with ischemic stroke. Even in rat models of stroke and TBI, there are clear differences in the fraction of animals developing epilepsy and the latent period to the first spontaneous seizure (Pitkänen et al., 2007). The latent period ranges from 1 to 6 months in TBI and stroke models, and only 50% (TBI) or 10 to 20% (stroke) of rats develop spontaneous seizures (Loescher and Brandt, 2010). This is strikingly

lower incidence compared to post-SE models where over 90% of rats develop epilepsy. However, SE is only a relatively rare cause of symptomatic epilepsy in humans. The long latent period and low percentage of rats developing epilepsy after stroke is a main disadvantage for preclinical studies, aside from even more laborious issues of EEG monitoring for several months. Consequently, there is no report of antiepileptogenesis study using stroke models is available. Analysis of the key papers on post-stroke epileptogenesis shows that there is very little data supporting any of the classic models leading to induction of chronic epilepsy (as opposed to short-term seizures). An important point made by Kelly and co-workers in at least two or three papers was that their initial observations of events that they thought were epileptic seizures were in fact spike-wave discharges that were readily seen in control animals. Thus, part of this probably reflects that the seizure frequency is extremely low and the seizures may occur in clusters, thus spontaneous epileptic seizures have not been well documented in these models.

Our understanding of the post-stroke disease process has benefitted greatly from established acute and chronic models. A combination of multidisciplinary neuroscience approaches involving stroke and epilepsy across gender and aged models offers a more integrated, system-level approach to address key questions in PSE. Although seminal insights and treatments have been identified from conventional rodent stroke models, there are many limitations of these rodent models that preclude effective advancement towards PSE modeling and validation of the therapeutic targets. Despite striking sex differences in stroke incidences, the bulk of PSE studies continue to be implemented in male animals. Embracing new technologies including rodent imaging and neuronal epigenome technology may provide broader approach to PSE modeling for pathology studies and drug discovery. Although tedious with limited success rates, embracing a wide range of animal models is helpful in our pursuit of a better understanding of the epileptogenic process triggered by the ischemic and hemorrhagic strokes.

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Abbreviations

AED	Antiepileptic drug
BBB	Blood-brain barrier
CCA	common carotid artery
CNS	central nervous system
CSF	cerebrospinal fluid
EEG	Electroencephalogram
ET-1	endothelin-1
MCA	middle cerebral artery

MRI	magnetic resonance imaging
PSE	post-stroke epilepsy
tPA	tissue plasminogen
TTC	triphenyltetrazolium chloride

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Significance

Stroke is a common cause of acquired epilepsy in the elderly. However, there is little progress in understanding the pathophysiology of post-stroke epilepsy (PSE). Currently, there are no specific drug therapies for preventing PSE in at-risk individuals. A greater understanding of PSE is required to facilitate the development of effective interventions for disease-modifying therapies for PSE. A clinically-relevant model is essential to understand the post-stroke epileptogenesis. We examined the currently available, limited array of models such as MCA occlusion and photothrombosis that are facilitating post-stroke modeling in animals. Embracing new imaging and epigenome technologies may accelerate post-stroke modeling for pathology studies and drug development.

Fig. 1. Middle cerebral artery (MCA) occlusion model of stroke in rats and mice
 (A) Site of MCA occlusion by intraluminal suture technique. (B) Diagrammatic representation of the MCA occlusion-induced damage (ischemic core) in the ipsilateral hemisphere along with the regions in the healthy contralateral hemisphere. *ACA*, anterior carotid artery; *BA*, basilar artery; *CCA*, common carotid artery; *ECA*, external carotid artery; *ICA*, internal carotid artery; *OCA*, ophthalmic carotid artery; *PCA*, posterior cerebral artery; *VA*, vertebral artery.

Fig. 2. Pathophysiology of post-stroke epilepsy (PSE)

PSE development can be described in three distinct stages: (i) the initial stroke injury (epileptogenic event); (2) the latent period (silent period with no seizure activity); and (3) chronic period with spontaneous recurrent seizures. Although the precise mechanisms underlying PSE remain unclear, the focal stroke damage activates diverse signaling events, such as inflammation, oxidation, apoptosis, epigenetic, neurogenesis and synaptic plasticity, which eventually lead to structural and functional changes in neuronal networks with enduring predisposition to synchronized hyperexcitability and seizures.

Fig. 3. Potential mechanisms of post-stroke epileptogenesis

Epileptogenesis after stroke stems from multifaceted pathways and signalling system in the brain, including chronic neuronal injury or neurodegeneration and neuroinflammation. Late-onset “epileptic” seizures after stroke are symptomatic manifestations of profound neuroanatomical changes in neural networks that control synchronized hyperexcitability. Such changes are evident progressively as a result of devastating acute neurovascular dysfunction and excitotoxicity that occur immediately after stroke.

Table 1

General profiles of selected post-stroke epilepsy models in adult male rats.

Feature	MCAO	Photothrombosis	Endothelin-1
Technical feasibility	Tedious	Simple	Simple
Mortality rate	Medium	Low	Low
Infarct volume	High	Low to High	Medium/high
Neurodegeneration	High	High	Medium/high
Neuroinflammation	High	High	High
Follow-up monitoring	2–10 months	4–10 months	2–12 months
Latency for seizures	2–8 months	2–4 months	2–10 months
Percent occurrence	0–25%	35–50%	0–8%
Seizure frequency	0.3/day	0.3/day	0.3/day
Seizure duration	115 s	75 s	80 s
Mossy fiber sprouting	None	Mild	Mild
Cognitive impairment	Present	Present	Absent
References	Karhunen et al., 2003; Kelly, 2006; Kelly et al., 2006	Kelly et al., 2001; Kharlamov et al., 2003; Karhunen et al., 2007	Karhunen et al., 2006

Table 2

Summary of post-stroke epilepsy animal models: surgical procedure, seizure occurrence, and characteristics.

Ischemia model	Rat strain	Sex/Weight	Damaged area	Surgical Procedure	Sz detection method	Follow-up time	% of animals w/ sz	Occurrence of sz	Sz duration	Ref
Transient MCAo (MCA + CCA)	Fischer 344 (age at ischemia 4 or 20 months)	Male 4 and 20 mo old	Cortex	Transient unilateral MCA/CCAO	EEG and visual (Racine)	2 mo	4 mo: 25% (1/4); 20 mo: 100% (5/5)	20 mo: 4 sz/wk	6 s to 1 min	Kelly (2006).
Transient MCAo	Sprague –Dawley	Male 275–315 g	Cortex, striatum	MCAo by filament method and reperfusion after 2 hours	continuous video-EEG recording for 1 week at 3, 7, and 12 months after MCAO	12 mo	0% (0/5)	—	—	Karhunen et al. 2003
Transient unilateral MCA/CCAO	Long-Evans	Male 2.5 mo old (323 ± 10 g)	Cortex	Transient focal ischemia induced by occlusion of the left MCA and left CCA. EEG implantation 2–3 wk after MCA/CCAO	Continuous video-EEG recording from ~1 mo post MCA/CCAO to 6 mo	6 mo	0% (0/7)	—	—	Kelly et al. 2006
ET-1	Sprague –Dawley	Male 275–315 g	Cortex, striatum	6 mo follow-up gr: Eic imp and ET1 on D0 12 mo follow-up gr: ET1 on D0, Eic imp on 11 mo	vEEG for 2 h (@2 h post ET-1) or 2 wk at 2, 4, 6, or 12 mo	6 mo or 12 mo	6 mo: 12.5 % (1/8); 12 mo: 0% (0/18)	0.21 sz/day	78–174 s	Karhunen et al. 2006
Cortical phototrombosis	Fischer 344 (age at ischemia 6 months)	Male at 2,6,12,24 and 30 mo old	Motor cortex	Rose Bengal to tail vein 80 mg/kg for 10 min	EEG and visual (Racine)	4 mo	50% (1/2)	no specific indication, “multiple”	90 s	Kelly et al. 2001
	Sprague –Dawley (age at ischemia 2 or 6 months)	Male at 2 and 6 mo old		Rose Bengal to tail vein 80 mg/kg for 10 min	EEG and visual (Racine)	8 mo	75% (3/4)	no specific indication	~13 s	Kelly et al. 2001
	Sprague –Dawley	young adult male	Primary somatosensory cortex of the hind limb	Rose Bengal dose and time vary	EEG and visual	4 mo	100% (2/2)	no specific indication, “daily recurrent”	~10 s	Liu et al. 2002
	Sprague –Dawley	Male 2 mo old		Rose Bengal in left femoral vein 30 mg/kg for 2 min	EEG and visual	6 mo	50% (5/10)	one sz every 4, 6 h	2–3 s	Kharlamov et al. 2003
	Sprague –Dawley	Male 2 mo old		Rose Bengal in left femoral vein 15 mg/kg or 30 mg/kg for 2 min	EEG and visual	2,4,6, 8,10 mo	18%	0.39 sz per recording day	117 s	Kharlamov et al. 2007
	Sprague –Dawley	Male 310–380 g (9–12 wk)		Rose Bengal to femoral or saphenous vein 20 mg/kg at 150 ul/min	EEG and visual (Racine)	10 mo	35%	0.26 sz/day	87 s	Karhunen et al. 2007