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Diabetic aggravation of stroke and animal models

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Abstract

Cerebral ischemia in diabetics results in severe brain damage. Different animal models of cerebral ischemia have been used to study the aggravation of ischemic brain damage in the diabetic condition. Since different disease conditions such as diabetes differently affect outcome following cerebral ischemia, the Stroke Therapy Academic Industry Roundtable (STAIR) guidelines recommends use of diseased animals for evaluating neuroprotective therapies targeted to reduce cerebral ischemic damage. The goal of this review is to discuss the technicalities and pros/cons of various animal models of cerebral ischemia currently being employed to study diabetes-related ischemic brain damage. The rational use of such animal systems in studying the disease condition may better help evaluate novel therapeutic approaches for diabetes related exacerbation of ischemic brain damage.

Keywords

Global cerebral ischemia; focal cerebral ischemia; stroke; translational research; preclinical models; hemorrhage; white matter damage

1. Introduction

Diabetes mellitus (referred to as diabetes below) is a serious metabolic disease associated with chronic hyperglycemia due to either a low production of insulin associated with improper functioning of pancreas, or a compromised insulin activity, linked with blunting of transduction mechanisms of insulin in the body. Type 1 diabetes (T1D) is characterized by a significant reduction in β -cell density in Islets of Langerhans and results in diminished production of insulin (Atkinson, 2012; Hansen et al., 2015; Kloppel et al., 1985). In a sub-

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set of T1D, autoimmune reactions destroy β cells in the islets of Langerhans (Atkinson, 2012; Hansen et al., 2015). Another cause of T1D is viral infection-induced destruction of β cells (Antonelli et al., 2014; Craig et al., 2013). Type 2 diabetes (T2D), occurs in most of the remaining diabetics (Amos et al., 1997). In T2D, there is a progressive increase in glucose intolerance and peripheral insulin resistance caused by improper diet, low exercise, obesity, and genetic predisposition (Weyer et al., 1999). Generally, T2D is considered adult-onset diabetes (Centers for Disease Control and Prevention, 2011). However, the prevalence of T2D in pediatric patients is increasing with time (American Diabetes Association, 2000; Centers for Disease Control and Prevention, 2011; Dabelea et al., 2014; Ehtisham et al., 2004; Fagot-Campagna, 2000; National Paediatric Diabetes Audit Project Board Royal College of Paediatrics and Child Health, 2013). These observations are in consonance with previously published studies (Harron et al., 2011; Holden et al., 2013; NHS Digital, 2016). It has been shown that insulin is used to treat a large section of young patients suffering from T2D in US (Rapaport et al., 2004; Silverstein and Rosenbloom, 2000).

An estimated 415 million people had diabetes in 2013, and this figure is expected to reach 642 million by 2040 (Guariguata et al., 2014; International Diabetes Federation, 2015). Cardiovascular disease is one of the most prominent disease resulting in deaths in more than half of diabetic individuals (Morrish et al., 2001). Further, diabetic subjects are almost two to three times more likely to suffer an ischemic stroke than non-diabetic subjects, and thus an increase in associated morbidity (Almdal et al., 2004). Diabetics have substantially increased age-adjusted stroke mortality and morbidity rates compared to non-diabetics (Barrett-Connor and Khaw, 1988). Available standard therapeutic strategies such as anti-hypertensive drugs, antiplatelet agents and, hypolipidemic drugs demonstrate therapeutic efficacy on reducing the risk of ischemic stroke in diabetics (Phipps et al., 2012). However, such treated diabetic individuals continue to suffer from cerebrovascular accidents despite receiving therapy as compared to non-diabetics (Mackenzie et al., 2013; Wang and Reusch, 2012; Zhao et al., 2013). MacDougall and Muir performed a systematic review of available literature on the effect of streptozotocin and dextrose induced acute hyperglycemia on focal cerebral ischemia induced infarction in brain. Their article shows that hyperglycemia enhances the size of ischemic infarct in brain and thus supports the view that hyperglycemia is a key factor which causes aggravation of ischemic brain injury in subjects suffering from T1D (MacDougall and Muir, 2011). Given the increase in number of diabetic people worldwide, increased incidence of cerebral ischemia in diabetics, and impact of diabetes on ischemic brain damage warrants the need to develop novel therapeutic approaches. Chen et al have shown that rats develop hyperglycemia, hyperinsulinemia, glucose intolerance, and insulin resistance after exposure to stroke (Chen et al., 2016). This suggests that besides the effect of diabetes on ischemic stroke-related brain damage, stroke also increases the risk of diabetes.

Employing appropriate animal models is critical in evaluating new therapeutic strategies. A comprehensive review detailing the various experimental systems available to study the disease may help researchers choose the appropriate model of cerebral ischemia and diabetes to study diabetes-induced increased ischemic brain damage. Therefore, in this review article, we provide an overview of the various animal models of cerebral ischemia used to study the effects of diabetes on ischemic brain damage.

1.1 Pathophysiology of Diabetes

T1D results from variety of factors including genetic, immunologic, and environmental resulting in degeneration of pancreatic β -cells leading to insulin deficiency. However, T1D is not evident until more than 70–80% of β -cells die (Powers, 2015). T2D is characterized by abnormal insulin secretion, insulin resistance, increase in glucose production in the liver, and altered fat metabolism. During initial progression of T2D, even during insulin resistance, normal glucose tolerance is observed due to compensatory increase in insulin production by β -cell. Eventually, hyperglycemia is observed when β -cells are not able to sustain increased insulin production to compensate increase in insulin resistance. After long-term T2D, patients eventually require insulin therapy for controlling hyperglycemia (International Diabetes Federation Guideline Development, 2014; Powers, 2015; Turner et al., 1999).

1.2 Pathophysiology of Stroke

Occlusion in the cerebral vasculature leads to a drop in blood flow in brain resulting in cerebral ischemia. The extent of drop of CBF (CBF) depends on vascular structure, status of collateral circulation, blood pressure and site of occlusion. Cerebral ischemia causes widespread infarction in brain (Smith et al., 2015). Three common mechanisms leading to ischemic stroke are: blockade in cerebral vasculature induced by an embolus formed somewhere else in the systemic circulation; thrombosis in cerebral vasculature causing blockade of small arterioles and; hypoperfusion due to stenosis of a major blood vessel in the cerebral vasculature (Smith et al., 2015). Once blockade of cerebral circulation is sufficiently prolonged and severe to cause cerebral infarction, neuronal cell death occurs by two modes: necrosis, which results from ischemic blockade of mitochondrial production of ATP in the cell, ion channel blockade, calcium influx and cellular depolarization induced excitotoxicity; and apoptosis, which is activated by multiple transduction mechanisms activated by ischemia (Smith et al., 2015).

2. STAIR criteria and diabetes research

The Stroke Therapy Academic Industry Roundtable (STAIR) research recommendations are a set of criteria laid down by academic and industry experts to ensure high translational value in stroke research. STAIR recommends the following criteria for assessment of novel therapeutic approaches for stroke: randomization, blinding, assessment of at least two outcomes, assessment in at least two species and in two or more laboratories, assessment of sex-related variations in efficacy, characterization of a clinically relevant route of administration, identification of a clinically useful therapeutic window, and establishing a dose-response relationship (Stroke Therapy Academic Industry Roundtable, 1999). STAIR guidelines in turn recommend that once a therapy is assessed in young healthy animals, it may be evaluated in aged animals and in animals suffering from other co-morbidities such as diabetes, hypertension and hypercholesterolemia (Stroke Therapy Academic Industry Roundtable, 1999). In support of these recommendations, diabetes and hyperglycemia are noted to increase mortality associated with incidence of stroke (Kiers et al., 1992). Therefore, evaluating the efficacy of protective therapy against cerebral ischemic damage using animal models of diabetes is of high clinical relevance.

3. Animal models of diabetes

When designing a study in diabetic animals, it is important to recreate the typical pathophysiological course of the disease in laboratory animals. Most often, this involves either the induction of diabetes in laboratory animals or the use of spontaneously diabetic animals (King, 2012; Like and Rossini, 1976; Nakhoda et al., 1977). Various animal models of diabetes are currently available and have been extensively reviewed by King (King, 2012). Besides, relevance of various animal models of diabetes with regard to their suitability in preclinical testing has also been discussed (King, 2012). Autoimmunity based destruction of β -cells in the pancreas is one of the pathogenic mechanisms of diabetes. The induction of diabetes by drugs toxic to pancreatic β -cells often serves as a reliable method of creating diabetic animals, albeit less representative of the mechanisms of the disease. Data shows that hyperglycemia causes decrease in cerebral plasma volume after ischemia which results in poor reflow induced cerebral infarction (Kawai et al., 1997). Venables et al have shown that acute hyperglycemia immediately after focal cerebral ischemia impairs reperfusion (Venables et al., 1985). Further, hyperglycemia decreases CBF after ischemia (Ginsberg et al., 1980; Kawai et al., 1997; Venables et al., 1985). Capes et al have observed that in comparison to diabetic subjects, nondiabetic subjects with ischemic stroke having hyperglycemia have an enhanced risk of 30-day mortality (Capes et al., 2001). Moreover, it was observed that acute hyperglycemia, in subjects suffering from ischemic stroke, correlates with greater infarct size and worse functional outcome independently of the diabetic status of the subjects (Parsons et al., 2002). Therefore, hyperglycemia appears to play an important role in exacerbating ischemic brain damage possibly via modulating cerebral vasculature (Martini and Kent, 2007). Use of models of chemical induced diabetes are appropriate for studies involving assessment of therapeutic systems which lower blood glucose levels without affecting β -cell functions. Streptozotocin and alloxan are pancreatic β -cell toxins effective in inducing diabetes with a single or multiple doses in laboratory animals (Black et al., 1980; Dave and Katyare, 2002; Ijaz et al., 2009; Kodama et al., 1993; Satav et al., 2000; Tancrede et al., 1983). Besides hyperglycemia, studies also observed ketoacidosis after induction of streptozotocin-induced T1D (Lam et al., 2005; Pan et al., 2001; Yuen et al., 2008). Antibodies against insulin have been used to induce diabetes in guinea pigs (Moloney and Coval, 1955).

Spontaneously diabetic animal models closely mimic the pathophysiological characteristics of diabetes and related complications. Several animal models are available which demonstrate genetic predisposition for developing autoimmunity-induced T1D. These include inbred BioBreeding rats (BB rats), Wistar Bonn/Kobori rats (WBN/Kob rats), a T1D rat model which arose through a spontaneous mutation in a congenic Lewis rat strain with a defined MHC haplotype (LEW.1AR1/Ztm-iddm rats), Akita mice, and non-obese diabetic mice (NOD mice) (Kalani et al., 2015; Lenzen et al., 2001; Nakama et al., 1985; Serreze and Leiter, 1994; Yagihashi et al., 1993; Yale and Marliss, 1984).

BB rats were generated by crossing two founder colonies suffering from spontaneous autoimmune diabetes viz., inbred BBDP/Wor and outbred BBdp rats (Song and Hardisty, 2009). Besides, diabetes resistant BB rats are also available which can serve as controls. In case of BB rats, diabetes typically develops around 80–100 days of age, and this model

shares severe ketosis and equal sex preference with the human disease (Nakhooda et al., 1978; Yale and Marliss, 1984). Disadvantages of this model include requirement of insulin for survival, lymphopenia (Song and Hardisty, 2009), and absence of peri-insulinitis. However, the merits of this model include its successful usage in delineating the genetics of T1D (Wallis et al., 2009), intervention studies (Hartoft-Nielsen et al., 2009), islet transplantation tolerance induction studies (Song and Hardisty, 2009) and studies of diabetic neuropathy. By contrast, WBN/Kob rats have relatively late onset of the disease (mean age of onset between 9 to 17 months), and in addition to diabetic symptoms these rats are also afflicted with neuropathy (Nakama et al., 1985; Yagihashi et al., 1993). Since they develop diabetes slowly, they do not need insulin for survival (Ishizaki et al., 1987). They are used for studying secondary complications of diabetes (Ishizaki et al., 1987).

LEW.1AR1/Ztm-iddm rats is a spontaneous rat model of T1D which arose from a natural mutation in a colony of congenic Lewis rats with a defined MHC haplotype, have about a 20% incidence rate with no sex preference (Lenzen et al., 2001) (mean age of onset: 58 ± 2 days). Moreover, additional inbreeding increases the incidence of diabetes to 60% in both genders (Jorns et al., 2005). Advantages include that besides demonstrating the presence of autoimmunity T1D, LEW.1AR1/Ztm-iddm rats do not show simultaneous presence of other autoimmune diseases and survive after onset of diabetes and thus may be employed to study secondary complications of diabetes. Secondly, presence of a pre-diabetic period facilitates studying time course of changes in infiltration of immune cells (Jorns et al., 2005).

Among NOD mice, induction of diabetes occurs preferentially in female animals as compared to their male counterparts. They exhibit mild ketosis, and their susceptibility to diabetes depends on an autoimmune reaction against the pancreas (Kataoka et al., 1983; Makino et al., 1980; Serreze and Leiter, 1994). Induction of diabetes is interfered by microbial contamination. Therefore, disadvantage include requirement of clean environment for proper development of diabetes. Secondly, different propensity of sexes to develop diabetes makes the model more expensive. However, different variants of the NOD mouse model of diabetes are available, which allows control over the timing of autoimmunity based-induction of diabetes, like cyclophosphamide-induced accelerated induction of diabetes, administration of T-cells from diabetic NOD mice to non-diabetic NOD mice and transplantation of syngeneic islets from young non-diabetic NOD mice into diabetic NOD mice (Caquard et al., 2010; Christianson et al., 1993; Rydgren et al., 2007). NOD mice are employed in studies evaluating therapy affecting autoimmune response-induced induction of diabetes (von Herrath and Nepom, 2005).

The AKITA mice were derived from C57BL/6NS1c mouse with a spontaneous mutation in the *insulin 2* gene that interrupted the processing of pro-insulin and caused endoplasmic reticulum stress leading to T1D after 3 to 4 weeks of age. However, the down side is that homozygotes carrying both copies of the mutant gene do not survive after 12 weeks, if left untreated (Mathews et al., 2002). AKITA mice serves as an alternate to streptozotocin-treated mice in transplantation studies and as a model of T1D-related macrovascular disease (Mathews, 2005; Zhou et al., 2011). Besides, other models of T1D use viruses as agents to induce diabetes like coxsackie B virus, encephalomyocarditis virus, and Kilham rat virus

(Craighead and McLane, 1968; Guberski et al., 1991; Jaidane et al., 2009; Kang et al., 1994; Yoon et al., 1986). For more details, please refer to a recent review (King, 2012).

There are multiple other spontaneously diabetic animal models available such as the Lep^{ob/ob} mice, Lepr^{db/db} mice, Kuo Kondo (KK) mouse, the Zucker Diabetic Fatty rat, the Goto-Kakizaki rat and Otsuka Long-Evans Tokushima Fat (OLETF) rats, representing a spectrum of the characteristics of T2D (Janssen et al., 2004; Lindstrom, 2007; Miyamoto et al., 1996; Nakamura and Yamada, 1967). The Lep^{ob/ob} mice is a monogenic model of T2D that is genetically deficient in leptin (Zhang et al., 1994). Leptin deficiency leads to hyperphagia and resultant obesity at 2–4 weeks of age. The mice then develop hyperglycemia reaching a maximum level between 3–5 months of age followed by a decrease to levels seen in lean control litter mates by 7 months of age (Edvell and Lindstrom, 1995; Westman, 1968). The volume of pancreatic islet is substantially increased in these mice (Bock et al., 2003). Moreover, they suffer from hyperlipidemia (Westman, 1968). Lepr^{db/db} mice are genetically deficient in leptin receptor (Chen et al., 1996) and are hyperphagic, are hyperinsulinemic by 2 weeks of age, develop obesity between 3–4 weeks of age, hyperglycemic between 4–8 weeks of age and become ketotic within a few months of age (Berglund et al., 1978; Coleman and Hummel, 1974). Besides being useful in studying the pathogenesis of T2D and diabetic dyslipidemia, these mice are employed for the assessment of insulin mimetic drugs (Zhang et al., 1999).

The KK mouse with inherent glucose intolerance, insulin resistance, and obesity serves as a model for obese T2D (Nakamura and Yamada, 1967). A derivative of KK mouse was created by incorporation of yellow obese A^Y gene into KK-A^Y mice (Chakraborty et al., 2009). Obesity observed with age is an advantage of this model. Secondly, hyperinsulinemia and hypertrophy of the pancreatic islets is also observed (Chakraborty et al., 2009). Other obese diabetes models include the leptin-resistant Zucker Diabetic Fatty rats. These rats develop diabetes only when there is a simultaneous induction of β -cell defect and obesity making this model more relevant to mimicking development of diabetes in humans (Griffen et al., 2001). Goto-Kakizaki rat is a non-obese model of T2D derived by selective inbreeding of Wistar rats with compromised glucose tolerance (Goto et al., 1976). A review article showed that there are similarities between changes in pancreatic β -cells in T2D subjects and Goto-Kakizaki rats (Portha et al., 2009). Moreover, Goto-Kakizaki rats are known to model secondary complications of diabetes such as retinopathy and neuropathy in terms of retinal microcirculatory alterations, glomerular hypertrophy and renal basement membrane thickening (Janssen et al., 2004; Miyamoto et al., 1996; Phillips et al., 2001). OLETF rats were derived from spontaneously diabetic rats from an outbred colony of Long Evans rats characterized by mild obesity and late onset hyperglycemia associated with progressive degeneration of pancreatic islets (Kawano et al., 1994).

Polygenic models of diabetes that demonstrate obesity and glucose intolerance along with diabetes serve to better mimic human disease condition. These models allow assessment of a number of genotypes. However, the limitation is that appropriate controls are not always feasible and male sex bias exists (Leiter, 2009). Besides, there are other models of T2D like New Zealand Obese mice, TallyHo/Jng mice, NoncNZO10/Ltj mice and high fat diet induced obese C57BL/6 mice which are described in detail by King earlier (King, 2012).

Each model reflects a different set of symptoms and pathological events seen in human diabetes. Therefore, for gaining a more complete understanding of cerebrovascular complications during human diabetes, it is important to select a model based on the relevance of that particular model with regard to the hypothesis being evaluated.

4. Animal models of diabetes used in studies of cerebral ischemia injury

Different animal models of diabetes have been employed to study effects of ischemia on the brain during diabetes (Table 2). The rat model of streptozotocin-induced diabetes is most often used to study effects of T1D on ischemic brain damage. Focal cerebral ischemia has been shown to induce larger extent of necrosis and apoptosis in streptozotocin-diabetic rats compared to non-diabetic controls (Britton et al., 2003; Li et al., 2004; Rizk et al., 2007; Rizk et al., 2005; Rizk et al., 2006). The BB rat model of spontaneous T1D has been used to study the effect of ischemia on a diabetic brain with a view of identifying the influence of factors such as high energy phosphate metabolism and tissue acidosis on the observed damage in brain (Sutherland et al., 1992; Toung et al., 2000). A model based on combination of low-dose streptozotocin and high-fat diet (Ding et al., 2017) has been employed to study the efficacy of investigational therapeutic approaches against T2D-induced enhancement of ischemic brain damage. The contribution of neutrophil-mediated inflammatory processes in worsening reperfusion injury during diabetes has been demonstrated using experiments on Zucker Diabetic Fatty rats (Ritter et al., 2011). Increased hemorrhagic transformation has been observed during stroke using T2D model Goto-Kakizaki rats (Ergul et al., 2007; Li et al., 2013). Assessment of CBF in Otsuka Long Evans Tokushima Fatty (OLETF) rats has shown diabetes causes ischemia-related alterations in CBF (Wajima et al., 2010). The KK-Ay mouse, diabetic db/db mouse and C57BL/6J ob/ob mouse are few of the spontaneously diabetic rodent models used in stroke studies (Iwanami et al., 2010; Kumari et al., 2011; Mayanagi et al., 2008). A study using focal cerebral ischemia in db/db mouse has identified the role of cerebral edema and inflammation in T2D-related aggravation of ischemic brain damage (Tureyen et al., 2011). Further, anti-diabetic drugs belonging to the class thiazolidinediones have been shown efficacious in treating pronounced ischemic damage in T2D db/db mouse (Tureyen et al., 2007). Several groups have studied the effect of cerebral ischemia in Zucker Diabetic Fatty rats (Kawai et al., 2011; Osmond et al., 2010; Ritter et al., 2011; Zhang et al., 2011). Therefore, a number of animal models of chemically-induced diabetes and spontaneous diabetes are used in preclinical efficacy studies to test potential therapeutic interventions for diabetic aggravation of ischemic brain injury.

Attenuation of cerebral ischemic damage by dextrose injection induced acute hyperglycemia is reported (Ginsberg et al., 1987; Kraft et al., 1990; Prado et al., 1988; Zasslow et al., 1989). Data also demonstrate that streptozotocin-induced acute hyperglycemia 2 days prior to ischemia decreases brain damage seen in the MCAO model of stroke (Nedergaard et al., 1987). However, other studies also have reported exacerbation of ischemic brain damage with hyperglycemia (Bomont and MacKenzie, 1995; de Courten-Myers et al., 1989; Duverger and MacKenzie, 1988; Huang et al., 1996; Kittaka et al., 1996). Besides, MRI studies have also shown that hyperglycemia increases ischemic brain injury (Li et al., 2004; Quast et al., 1997; Wei et al., 2003). Overall, most of the basic and clinical studies indicate that hyperglycemia causes increase in ischemic brain damage.

5. Animal models of stroke

Stroke is a multifactorial disease and thus requires different animal models to understand the disease (Ginsberg and Busto, 1989). Animal models of cerebral ischemia are broadly classified as ischemic (global, focal, and multifocal), and hemorrhagic (Ginsberg and Busto, 1989). A global ischemic insult in brain, caused by cardiac arrest or equivalent conditions, results in delayed neuronal degeneration in the CA1 hippocampus and frontal neocortical region (Horn and Schlote, 1992). Global cerebral ischemia involves reduction in CBF in many parts of the brain and successfully mimics the clinical condition of cardiac arrest-related neuronal damage in brain. A model of global cerebral ischemia has been used to understand the metabolic alterations associated with ischemic damage during diabetes (Levy et al., 2004). The two-vessel occlusion model of forebrain ischemia is one of the most characterized and widely used models of global cerebral ischemia (Table 1).

Focal cerebral ischemia involves reduction in blood flow to a part of the brain that is usually affected during ischemic stroke. The most common form of focal ischemic stroke results from the occlusion of the middle cerebral artery (MCA) (Bederson et al., 1986). Therefore, a method of inducing clinically relevant focal cerebral ischemia is to occlude the MCA with a thread, which bypasses open-skull surgery (Longa et al., 1989). While transcranial surgical occlusion-based approaches (clamps, ligation, etc.) are able to induce focal cerebral ischemia, these suffer from the limitations of involving surgical and open skull trauma (Krafft et al., 2012; Ringelstein et al., 1992; Robinson et al., 1975; Tamura et al., 1981a, b). Neither method of artificial occlusion models thromboembolism and thrombolysis (Liu and McCullough, 2011). Although the lack of thromboembolism and thrombolysis renders models less analogous to human stroke, certain experiments solely require ischemia as a variable rather than the entire condition of stroke. Induced embolism models thrombus-based elicitation of stroke, but stroke induction is variable, and even so, infarction location is difficult to control (Kudo et al., 1982; Toomey et al., 2002; Zhang et al., 1997). Sun et al have reported use of a novel model of transient hypoxia-ischemia-induced thrombotic ischemic stroke in mice by reversible ligation of the unilateral common carotid artery along with inhalation of 7.5% oxygen for 30 min. Although common carotid artery occlusion causes cerebral hypoperfusion, hypoxia-ischemia is noted to cause thrombosis-induced ischemic brain damage, which is reduced by tPA therapy (Sun et al., 2014).

Two subtypes of hemorrhagic stroke constitute the remaining cases of stroke. Intracerebral hemorrhage (ICH) occurs within the brain tissue (Broderick et al., 1993). Models attempt to recreate or emulate hemorrhage by injecting autologous blood or bacterial collagenase into the rat striatum (MacLellan et al., 2006; MacLellan et al., 2008). This procedure requires a small craniotomy. A different model involves induction of intra-ventricular hemorrhage by infusing venous blood into the lateral ventricles of week-old rats (Chen et al., 2010). The other subtype of hemorrhagic stroke, subarachnoid hemorrhage (SAH), involves bleeding in the subarachnoid space between the arachnoid membrane and pia mater around the brain. SAH can be induced with intracisternal autologous blood injection (Solomon et al., 1985). This model controls the amount of blood injected. Another variant of the same model in rat involving double cisterna magna injection is proposed to mimic the time course of the disease (Guresir et al., 2015). Alternatively, perforation of the internal carotid artery also

closely resembles the human aneurysm (Veelken et al., 1995). Models for both types of hemorrhage result in neurodegeneration, the severity of which varies with the procedure (Germano et al., 1994; Hartman et al., 2009; Thal et al., 2008).

6. Animal models of cerebral ischemia used to study effects of diabetes

Various groups around the world are using different models of stroke to study diabetic exacerbation of ischemic brain damage. In order to identify the contemporary use of various available models of cerebral ischemia to study diabetes-related aggravation of ischemic brain damage, we performed a literature search. Table 1 shows the frequency with which different stroke models are used to study the pathological condition. The literature search was carried out using PubMed by searching for ‘models of cerebral ischemia and diabetes’, ‘hemorrhage and brain and diabetes and animal’, ‘subarachnoid hemorrhage and diabetes and animal’, and ‘cardiac arrest and diabetes and animal’ keywords (performed on February 2, 2017). Table 2 summarizes the information regarding the disease pathophysiology mimicked by various models, their clinical relevance and a note regarding the usage of different animal models in diabetic stroke research.

6.1 Models of global cerebral ischemia

Diabetics are prone to a high risk of cardiac arrest primarily due to cardiovascular complications associated with a more progressive development of atherosclerotic plaques in the coronary arteries (Siscovick et al., 2010). Diabetes exerts a similar detrimental effect on cerebrovascular circulation by virtue of its influence on facilitating atherosclerosis in the carotid arteries (Fabris et al., 1994; Friedlander and Maeder, 2000). Eighty four percent of diabetics above 65 years of age die of cardio/cerebrovascular disease, chiefly heart disease (68%) and stroke (16%) (Mozaffarian et al., 2016; National Diabetes Fact Sheet, 2011). Diabetic subjects suffering from cerebrovascular complications demonstrate more pronounced neurological deficits, disability, recurrence and a poorer long-term prognosis in comparison to their non-diabetic counterparts (Elneihoum et al., 1998; Megherbi et al., 2003; Parsons et al., 2002; Ribo et al., 2005; Sprafka et al., 1994). Ischemia models involving the induction of global cerebral ischemia by ligating the carotid and vertebral arteries or carotid arteries are reported to resemble the clinical condition of ischemic brain damage during cardiac arrest or coronary occlusion in humans (Eklof and Siesjo, 1972a, b; Lim et al., 2004; Pulsinelli and Brierley, 1979). The role of inflammatory mechanisms, associated damage to astrocytes and activation of apoptosis play a role in diabetic aggravation of stroke using global cerebral ischemia model in streptozotocin-diabetic rats (Ding et al., 2004, 2005; Jing et al., 2013b; Jing et al., 2014; Li et al., 1998; Muranyi et al., 2006). Further, use of global cerebral ischemia model in rats has demonstrated the detrimental effect of estrogen replacement therapy on ischemic brain damage among diabetic females (Shen et al., 2010; Xu et al., 2004; Xu et al., 2006; Xu et al., 2009).

6.1.1 Two-vessel occlusion model of forebrain ischemia—The two-vessel occlusion (2-VO) model of global cerebral ischemia ensures generation of forebrain ischemia followed by complete reperfusion. In this model, transient severe forebrain ischemia is induced by bilateral carotid artery occlusion (for a period of 5–15 minutes) along

with systemic hypotension sufficient to substantially reduce blood supply to the forebrain (Eklof and Siesjo, 1972a, b; Nordstrom et al., 1978). Eklof and Siesjo have shown that adequate hypotension is critical to ensure bilateral carotid artery occlusion-induced reduction in CBF to an ischemic range ($<5\%$ of control in the cerebral cortex, $<15\%$ of control in the caudoputamen, hippocampus, and cingulate cortex) (Kagstrom et al., 1983). Optimal hypotension during the induction of two vessel occlusion-induced incomplete global cerebral ischemia can be achieved either by exsanguination, or by inducing hemorrhage along with the administration of systemic blood pressure lowering drugs such as trimethaphan or phentolamine (Kagstrom et al., 1983; Nordstrom et al., 1978; Smith et al., 1984a; Smith et al., 1984b). In the 2-VO model, ischemia and reperfusion are almost immediately followed by a transient reduction in CBF (Kagstrom et al., 1983; Smith et al., 1984b). A 2-VO model of global cerebral ischemia results in substantial damage to certain sensitive areas of brain, such as hippocampal CA1 pyramidal neurons and cells in the caudoputamen and neocortical areas (Smith et al., 1984b). Using the 2-VO model, the severity of cerebral ischemia and thus extent and distribution of neuronal damage can be controlled by varying the duration of bilateral carotid artery occlusion (Smith et al., 1984a). Among the principal models of global cerebral ischemia, the 2-VO model involves relatively simple surgical methodology and complete reperfusion, resulting in easy employment for experiments requiring survival. However, seizures may occur immediately after longer periods of ischemia induced by the 2-VO (Smith et al., 1984b). Durham et al observed impaired contextual fear conditioning response following 2-VO indicating that assessment of fear conditioning response may serve as a tool to evaluate functional outcome post-ischemia (Durham et al., 2012). Various groups have employed the 2-VO model of forebrain ischemia (with or without modifications) in studying the detrimental consequences of diabetes on ischemic brain damage (Fujii et al., 1992; Wajima et al., 2010) and the potential neuroprotective effect of test drugs on diabetes-induced aggravation of ischemic neuronal injury (Prabhakar, 2013; Wajima et al., 2011). Using this model, we observed that prior exposure to recurrent hypoglycaemia markedly enhanced cerebral ischemic injury in diabetic rats (Dave et al., 2011).

6.1.2 Four-vessel occlusion model of forebrain ischemia—The four-vessel occlusion (4-VO) model of global cerebral ischemia ensures the generation of reversible high grade forebrain ischemia in awake, freely moving or anaesthetized rats resulting in a prominent reduction in CBF and culminates in reproducible ischemic neuronal changes in various parts of the brain ($<3\%$, $<3-7\%$, and $<10-15\%$ of blood flow seen in non-ischemic sham control in striatum and neocortex, hippocampus, and diencephalon and cerebellum, respectively) (Ginsberg and Busto, 1989; Pulsinelli et al., 1982; Schmidt-Kastner et al., 1989). Generation of cerebral ischemia using the 4-VO model involves two phases: in phase I, rats undergo permanent bilateral vertebral artery occlusion via electrocauterization on day 1; in phase II rats undergo transient bilateral carotid artery occlusion for a period of 10 to 30 minutes between 2–5 days of the bilateral vertebral artery occlusion procedure (Pulsinelli and Brierley, 1979; Schmidt-Kastner et al., 1989). Induction of mild hypotension (80–90 mm Hg) is reported to decrease variability of outcome by avoiding initial hypertension caused by common carotid artery occlusion during phase II (Globus et al., 1988a, b). A principal characteristic of this model is that with the sudden drop in CBF, a profound

hyperemia is observed after a few minutes of reperfusion, followed by a sharp decrease in CBF which may be long lasting in certain areas of the brain (Pulsinelli et al., 1982).

Widespread neurodegeneration is seen in the 4-VO model. While 30 minutes of 4-VO induces ischemic damage in the striatum and thalamus, the extent of hippocampal damage directly depends on the duration of ischemia (Pulsinelli and Brierley, 1979; Pulsinelli et al., 1982). This animal model has been successfully employed to evaluate morphological as well as metabolic changes linked to severe ischemia in anesthetized rats (Dietrich et al., 1984; Globus et al., 1988b; Yoshida et al., 1982). The behavioural outcome measures used in the 4-VO studies include spatial memory assessment using Morris water maze test, Sidman avoidance task and Barnes maze test (Kawaguchi et al., 2014; Meilin et al., 2014; Raz et al., 2010; Samson et al., 2010).

The principal limitations of the 4-VO model are: cumbersome surgical procedure (leading to a low survival rate), occurrence of seizures, and variable results in different strains of animals (Ginsberg and Busto, 1989; Schmidt-Kastner et al., 1989). Some investigators have successfully employed the 4-VO model of forebrain ischemia to evaluate the neurotransmitter alterations leading to diabetes-associated damage of the ischemic brain (Guyot et al., 2000, 2001).

6.1.3 Cardiac arrest and resuscitation—The latest advancements in methods of treating cardiac arrest have enhanced survival but neurological impairment remains largely untreatable (Athanasuleas et al., 2006; Hashiguchi et al., 1993). Further, diabetes mellitus is identified as one of the most important risk factors that exacerbates the prognosis of cardiac arrest-related neurological damage and mortality (Valles et al., 2006). The cardiac arrest and resuscitation model of global cerebral ischemia produces transient complete ischemia of the whole body followed by resuscitation-based revival (Hendrickx et al., 1984; Katz et al., 1995). Mild cardiac arrest results in long-term behavioral deficits when assessed using behavioural tests like Y Maze test and open field test (Schreckinger et al., 2007). In the light of epidemiological data showing a high frequency of cardiac arrest among diabetics and non-diabetics, this model promises to study brain damage associated with cardiac arrest among diabetics (Hoxworth et al., 1999; Valles et al., 2006). Concomitant occlusion of the right atrium and aorta, generalized asphyxia, potassium chloride treatment and electric current delivery are some of the techniques employed to induce cardiac arrest (Chen et al., 2007a, b; Crumrine and LaManna, 1991; Dave et al., 2013; Dave et al., 2004; Hossmann et al., 2001; Katz et al., 1995; Kawai et al., 1992; Krajewski et al., 1995; Pichiule et al., 1999; Pluta et al., 1994; Reid et al., 1996; Studer et al., 2005; von Planta et al., 1988). While Hoxworth et al. used intra-arterial infusion of D-tubocurarine and ice cold potassium chloride to induce cardiac arrest, Wagner and Lanier induced cardiac arrest by potassium chloride infusion to study the effects of diabetic hyperglycemia on brain metabolism during ischemia (Hoxworth et al., 1999; Wagner and Lanier, 1994). However, the principal limitation of cardiac arrest-induced cerebral ischemia is the requirement of intensive post-operative care.

6.2 Models of focal cerebral ischemia

Focal cerebral ischemia involves the cessation of blood flow to a particular region in the brain mostly supplied by a given artery. More than half of patients suffering from stroke are affected by ischemia in the vascular region of brain receiving blood via the MCA (del Zoppo et al., 1992). Therefore, a majority of the research groups studying ischemic stroke employ the middle cerebral artery occlusion (MCAO)-based models of focal cerebral ischemia. Studies by a group have used the model of focal cerebral ischemia in streptozotocin-diabetic rats to identify the role of astrocytes in diabetic exacerbation of ischemic brain damage and the activation of apoptotic cell death mechanisms thereof (Jing et al., 2013a; Muranyi et al., 2003). Moreover, a considerable correlation has been reported between MCA stenosis and diabetes mellitus (Telman et al., 2015). It has been shown that among the diabetes patients suffering from stroke, mortality in those subjects having MCA involvement is significantly higher than their respective controls (Arboix et al., 2005). Further, transcranial Doppler examination-based studies have shown that, among Chinese patients, 20.6 % of patients suffering from T2D possess MCA stenosis and are thus more prone to suffer a life-threatening form of stroke than other subjects (Thomas et al., 2004; Wong et al., 2000). Therefore, the MCAO-based focal cerebral ischemia model of stroke is considered one of the most clinically relevant models to mimic the condition of stroke among diabetics. MCAO models to induce focal cerebral ischemia involving either a permanent or a transient blockade of CBF through the MCA by either occluding the proximal or distal aspect of the artery are among the different forms of MCAO induction procedures (Belayev et al., 1996; Fang et al., 2016; Garcia, 1984; Wayman et al., 2016).

6.2.1 Transcranial surgical MCAO—The transcranial surgical MCAO model is a method of proximal MCA occlusion which ensures reproducible generation of a consistent lesion in the rodent brain particularly in the cortex and caudoputamen areas (Bederson et al., 1986; Ginsberg and Busto, 1989; Tamura et al., 1981a). Such induction of cerebral damage is known to mimic clinical conditions of ischemic hemispherical infarction in humans associated with a consistent reduction in blood flow to the region of brain supplied by the MCA (<10% of control in the hippocampus, hypothalamus and thalamus, <15–20% of control in the neocortex and lateral part of the neostriatum, and <20–40% of control in the medial thalamus, ventral thalamus, ipsilateral nucleus accumbens, and medial portion of the neostriatum) (Tamura et al., 1981b). This model offers a direct control over the site of occlusion (Akamatsu et al., 2015; Krafft et al., 2012; Ringelstein et al., 1992; Robinson et al., 1975; Tamura et al., 1981a, b). The surgical procedure in this model typically involves sub-temporal craniotomy-based isolation of MCA followed by its occlusion at the aspect proximal to the olfactory tract (Bederson et al., 1986; Krafft et al., 2012; Tamura et al., 1981a, b). However, the disadvantage of this model is the necessity of craniotomy (Krafft et al., 2012). With a view of minimizing the invasive nature of surgery involved in this model, Chen et al (Chen et al., 1986) have introduced a model involving transcranial surgical MCAO along with transient ipsilateral common carotid artery occlusion. A focal ischemia study has shown that the extent of ischemic damage varies from batch to batch (Brint et al., 1988). Many behavioral outcome measures such as assessment of spatial memory disturbance using Morris water maze (Yonemori et al., 1996; Yonemori et al., 1999), quantification of motor deficit using rotarod test, spontaneous movement test and

neurological examination have been used in transcranial MCAO model (Yamamoto et al., 1988; Yonemori et al., 1998). However, validation of these measures as a reliable method of assessment after chronic transcranial MCAO is pending. Still, the transcranial surgical MCAO model of focal cerebral ischemia offers a feasible option while designing a study aimed at evaluating an agent for its activity on diabetes-linked aggravation of ischemic neuronal injury. Use of the transcranial surgical MCAO in cats has shown the detrimental effect of hyperglycemia on ischemic brain (de Courten-Myers et al., 1988; de Courten-Myers et al., 1994; Zasslow et al., 1989). Poittevin et al. employed the model of permanent left middle cerebral artery electrocoagulation to assess the effect of diabetes on cerebral vasculature (Poittevin et al., 2015). Further, Araki et al. have used the clip ligation method induced transcranial MCAO model to study the role of calcium in hyperglycemia-induced detrimental effect on ischemic brain (Araki et al., 1992).

6.2.2 Endovascular MCAO—Compared to the transcranial surgical model, the endovascular MCAO model of focal cerebral ischemia is a less invasive procedure to generate permanent (Fang et al., 2016; Mao et al., 2014) or transient MCAO (CBF of <20% of control in the cortex and caudoputamen) (Garbuzova-Davis et al., 2016; Longa et al., 1989; Memezawa et al., 1992). The method of the endovascular MCAO involves insertion of a suture into the internal carotid artery until it blocks the origin of the MCA and the collateral circulation from anterior communicating arteries (Longa et al., 1989). A Laser Doppler flow probe is typically placed on the brain tissue expected to be ischemic in order to confirm the fall in CBF, the principal hallmark of stroke / cerebral ischemia. Withdrawal of the intra-luminal suture is done to elicit reperfusion and functional outcome is measured at different time points thereafter (DeVries et al., 2001). Behavioral deficits are observed following mild transient MCAO when evaluated using lateralized stepping test, rotarod test, apomorphine-induced rotations test and the staircase task (Trueman et al., 2016). Besides, a study using Morris water maze test observed that T2D itself leads to cognitive deficits and these deficits are worsened post-MCAO (Zhang et al., 2009). A meta-analysis-based systematic review of research publications using the model of endovascular MCAO has shown that diabetic hyperglycemia is associated with a prominent increase in cerebral infarct size (MacDougall and Muir, 2011). Huang et al. (2014) have used the model of endovascular MCAO to show that diabetic animals have disturbed capillary blood flow and are thus more vulnerable to neurovascular abnormalities following cerebral ischemia. Moreover, hyperglycemia *per se* causes decrease in reperfusion blood flow by facilitating vasoconstriction (Martini and Kent, 2007). Further, various research groups have used the endovascular MCAO model to assess the benefit of different therapeutic strategies proposed to treat the enhanced neurodegeneration associated with stroke among diabetics (Briyal et al., 2012; Cui et al., 2012; Darsalia et al., 2014; Iwata et al., 2014; Simard et al., 2009; Song et al., 2014; Yan et al., 2013). The endovascular MCAO model has been used to study diabetic aggravation of ischemic brain damage in db/db diabetic mice (Chen et al., 2012; Chen et al., 2011) and SHR rats (Slivka, 1991). Using the mice model, Chen et al have further shown the therapeutic benefit of administering CXCR4-primed endothelial progenitor cells in diabetic animals (Chen et al., 2012; Chen et al., 2011). Furthermore, some mechanistic studies have employed the endovascular MCAO model to explore the pathways involved in mediating diabetes-related aggravation of ischemic brain damage

(Martin et al., 2006; Srinivasan and Sharma, 2012a, b; Wei et al., 1997; Wei and Quast, 1998). A study involving permanent and transient MCAO using the endovascular approach has demonstrated the worsening effect of hyperglycemia on the size of ischemic infarct (Liu et al., 2007). Disadvantages associated with this model include peri-surgical morbidity owing to extensive neck surgery, variability in infarct size because of the anatomical variation in the circle of Willis, and the extent of occlusion achieved. Another principal limitation of this model is that it fails to precisely mimic the cause of stroke among diabetics; i.e., thromboembolism (Howells et al., 2010). Overall, the endovascular MCAO appears to be an important and frequently employed animal model to study the pathogenesis of stroke during diabetes.

6.2.3 Thromboembolic MCAO—Eighty-seven percent of stroke patients suffer from ischemic stroke primarily owing to embolus formation which blocks the cerebral arteries, or else in situ thrombus formation in cerebral vasculature (Roger et al., 2012). Immediately after stable embolus or thrombus formation causes the occlusion of cerebral blood vessels, the supply of oxygen and glucose to some parts of the brain is reduced below a critical level which, if continued for a protracted period, results in a progressive loss of brain function seen during stroke (Roger et al., 2012). A heightened level of thromboembolism is noted in diabetic subjects having relatively less control over their hyperglycemia (Eyadiel et al., 2014; Lerstad et al., 2014; Tala et al., 2014). Naïve (non-diabetic) subjects suffering from acute ischemic attack are successfully treated with anticoagulant and/or anti-platelet drugs (Abdul-Rahim et al., 2015). The current status of success seen with drugs limiting the progression of thrombosis and embolus formation leading to stroke is encouraging (Abdul-Rahim et al., 2015; Burnette and Nesbit, 2001). However, these treatments are noted to be relatively less effective among diabetics (Piazza et al., 2012, 2014). Therefore, novel treatment methods for more effectively controlling mechanisms leading to thromboembolism are needed. In spite of variability in infarct size and distribution, thromboembolic occlusion of MCA-induced focal cerebral ischemia is one of the standard animal models of stroke. This model is employed to study thrombolytic interventions and approaches combining thrombolytic as well as neuroprotective drugs to treat the pathological condition of stroke *per se* (Overgaard, 1994; Zhang et al., 2004) and stroke during the co-morbid condition of diabetes (Ning et al., 2012; Ning et al., 2014). Another model involving sodium laurate injection into the MCA results in the generation of innumerable thromboemboli which consequently cause the production of multiple infarcts in hippocampus, cortex and thalamus (Toshima et al., 2000). Thrombi generation is achieved in the MCA by direct administration of various agents like thrombin (Zhang et al., 1997), human blood clot (Papadopoulos et al., 1987), photoactivated thrombogenic agents (Nagai et al., 2002; Watson et al., 1985; Watson et al., 1987), surfactants such as sodium laurate (Toshima et al., 2000), and carbon microspheres (Kogure et al., 1974). These methods are used to reproducibly generate small infarcts in defined areas of brain and are thus important models for studying the pathogenesis of cortical infarction. Despite Watson et al. have established that ultraviolet laser-mediated facilitation of recanalization can induce reperfusion in a rat model of photothrombotic stroke (Watson et al., 2002), this model is scarcely used to study the effect of reperfusion and thrombolysis *per se*. Various groups have employed these models to study the efficacy of novel therapeutic interventions on

detrimental effects of diabetes on ischemic brain damage (Ning et al., 2014; Simard et al., 2009). Bederson score of neurological deficit has been used to evaluate functional deficits in a model of thromboembolic MCAO (Bederson et al., 1986). Overall, the application of thromboembolic MCAO models of stroke holds great promise in terms of its potential to contribute toward the understanding of diabetic aggravation of ischemic brain damage.

6.3 Models of hemorrhagic stroke

Cerebral hemorrhage is a life-threatening form of cerebrovascular event known to affect 10% to 20% of patients suffering from stroke (Navas-Marrugo et al., 2014). ICH, a form of hemorrhagic stroke leading to a marked increase in mortality (mortality within one month is about 40%) and morbidity (most of the survivors become disabled), is an untreatable condition (van Asch et al., 2010). A meta-analysis-based report of multiple studies and another systematic review has shown that diabetes is a major risk factor for ICH (Ariesen et al., 2003; The Emerging Risk Factors Collaboration, 2010). Subjects suffering from diabetes are 1.6 times more likely to suffer a major ICH than their non-diabetic counterparts (Ariesen et al., 2003; The Emerging Risk Factors Collaboration, 2010). Besides, hemorrhagic transformation is observed more frequently in diabetic subjects than non-diabetics (Ariesen et al., 2003). A group has shown that in a model of focal cerebral ischemia (middle cerebral artery occlusion using micro-aneurysm clips), tPA-induced ICH is enhanced in streptozotocin-diabetic rats confirming clinical findings in an animal model (Won et al., 2011). Therefore, use of animal models of intracerebral and subarachnoid hemorrhages to study diabetes-induced enhancement of ischemic brain damage are appropriate and are being employed to study the pathological condition (Simard et al., 2014). Various forms of animal models of brain hemorrhage are currently available (Krafft et al., 2012).

6.3.1 Subarachnoid hemorrhage—Subarachnoid hemorrhage refers to internal bleeding, usually from a ruptured aneurysm, in the subarachnoid space around the brain. Multiple models are available to mimic the clinical condition of subarachnoid hemorrhage. Methods employed to elicit internal bleeding in the subarachnoid space between the arachnoid membrane and pia mater include perforation of the internal carotid artery with a monofilament suture (Veelken et al., 1995), and intracisternal administration of blood or blood components (Solomon et al., 1985; Suzuki et al., 1999). Studies have shown that the volume of blood leaked into the affected subarachnoid space, the consequent level of ischemic brain damage and the overall functional outcome are highly correlated (Thal et al., 2008). Both methods of induction of subarachnoid hemorrhage produce diffuse ischemic brain damage and thus cause sensorimotor and cognitive deficits, but only cognitive deficits last for a longer period of time owing to the virtual absence of ischemic neuronal injury to descending motor tracts (Germano et al., 1994; Silasi and Colbourne, 2009; Thal et al., 2008). This further strengthens the clinical relevance of the model, as a long-lasting cognitive decline is one of important problems faced by patients with subarachnoid hemorrhage (Bailes et al., 1990; Frazer et al., 2007; Hackett and Anderson, 2000; Lanzino et al., 1996). However, the endovascular perforation model of subarachnoid hemorrhage is associated with mortality rates from 37.5 % (monitored up to 3 h post-perforation) to 50 % (monitored up to 24 h post-perforation) (Bederson et al., 1995; Veelken et al., 1995).

6.3.2 Intracerebral hemorrhage—ICH has been shown to be elicited in laboratory animals by either defined enzymatic digestion of the cerebral vasculature, or parenchymal administration of autologous blood (or blood products) in rodents to mimic the consequences of human spontaneous ICH (Belayev et al., 2003; Bullock et al., 1984; Rosenberg et al., 1990). In this model, ICH is induced by performing a small craniotomy (using a burr hole device) followed by stereotactically guided injection of bacterial collagenase or blood (or blood products). Autologous blood administration-induced ICH in striatum is used to evaluate the pathogenesis of hemorrhagic brain damage and edema formation (Belayev et al., 2003; Yang et al., 1994). A model of collagenase-induced spontaneous bleeding in the brain tissue is used for determining efficacy of approaches to enhance post-ICH hemostasis (MacLellan et al., 2008; Xi et al., 1998). The principal advantage of this category of models is to present a robust sensorimotor deficit in animals, a phenomenon commonly seen in patients suffering from a similar clinical condition of ICH involving basal ganglia and thalamus (Hartman et al., 2009; Qureshi et al., 2001). Secondly, the collagenase injection model is also known to generate long-term neurofunctional deficits and so has been used more extensively than the blood injection model for studying rehabilitation approaches after ICH (Auriat and Colbourne, 2009; Auriat et al., 2010; MacLellan et al., 2010). Further, as compared to the blood injection model, the collagenase injection model is considered more appropriate for studying hematoma expansion and the extent of blood infiltration into the parenchyma (MacLellan et al., 2010). Moreover, the collagenase model provides better control over the degree of hemorrhage, and it may be employed for studying delayed cell death during ICH and for identifying the therapeutic window for agents promising to treat this devastating neurological disease (MacLellan et al., 2010). On the other hand, the blood injection model does not ensure continued bleeding, and when a large volume of blood is injected, the infused blood may come back up the needle injection path, resulting in a variable degree of damage (MacLellan et al., 2010).

Corner turn test, forelimb placing test, forelimb use asymmetry test and neurological severity score are few of primary behavioral parameters used to assess behavioral outcome of the neurological damage induced by experimental cerebral hemorrhage (Hua et al., 2002; Yang et al., 2012). However, a critical assessment of these measures in the context of chronic effects of hemorrhagic stroke in animals and its clinical homology may help us identify reliable tests for preclinical efficacy studies.

6.4 Models of white matter stroke

White matter constitutes a sizable portion of the central nervous system (Zhang and Sejnowski, 2000) and has been found to be vulnerable to even a mild ischemic stress (Irving et al., 2001; Pantoni et al., 1996). Stroke selectively affecting the white matter is noted to constitute 15 to 25% of stroke subtypes (Bamford et al., 1991; Schneider et al., 2004). Diabetes and hyperglycemia increase the extent of white matter lesion volume when compared to non-diabetic controls (Gouw et al., 2008; Jongen et al., 2007). Disruption of cells in white matter of brain are shown in T2D patients (Zhang et al., 2014a). In chronic hypoperfusion model white matter damage is seen (Yatomi et al., 2015). However, application of carefully designed and selected animal models is required to validate the pathological and therapeutic relevance of such a possibility. Animal models available to

explore the contributions made by white matter damage in ischemic stroke include: *in vitro* model of white matter ischemia like optic nerve anoxia/reoxygenation (Stys and Lesiuk, 1996; Waxman, 2008), focal white matter stroke models such as endothelin-1 induced vasoconstriction, anterior choroidal artery occlusion method, and also carotid artery occlusion/stenosis-induced white matter stroke, systemic hypertension models, and arteriopathy models (Frost et al., 2006; Hughes et al., 2003; Sozmen et al., 2012).

The *in vitro* model of optic nerve anoxia/reoxygenation is useful for assessment of white matter injury in the optic nerve and thus study neuroprotective effect of pharmacological agents. Additionally, an *in situ* model of optic nerve ischemia has been described to mimic the clinical condition of ischemic injury to white matter during stroke and spinal cord injury (Stys and Lesiuk, 1996). The focal model of white matter stroke elicited by endothelin-1 induced vasoconstriction is generated by an injection of endothelin-1 (ET-1), into the posterior limb of the internal capsule adjoining parietal cortex. Degeneration of a number of ascending fibers to the somatosensory cortex and descending fibers from motor cortex is associated with the development of infarct resulting from endothelin-1 administration. Sensory motor abilities are then tested using behavioral assessment. At the completion of the procedure, histological assessment of infarct size is carried out (Frost et al., 2006). Besides, white matter stroke can be successfully elicited by direct administration of a vasoconstrictor called N5-(1-iminoethyl)-L-ornithine into the subcortical white matter region in mouse brain (Hinman et al., 2013; Rosenzweig and Carmichael, 2013). Anterior choroidal artery occlusion method involves microinjection of ET-1 into certain areas of brain like cortex, striatum or sub-cortical white matter to generate focal ischemia in grey or white matter, without affecting the permeability of blood brain barrier. Resultant lesion is assessed using immunohistochemistry (Hughes et al., 2003).

Besides, studies have shown that chronic cerebral hypoperfusion associated with bilateral common carotid artery stenosis cause substantial white matter damage in rat and mouse models (Ni et al., 1995; Sarti et al., 2002; Shibata et al., 2004; Wakita et al., 1994). In this model, bilateral common carotid artery stenosis is induced by winding microcoils around the carotid arteries just below the carotid bifurcation (Khan et al., 2015; Ni et al., 1995; Sarti et al., 2002; Shibata et al., 2004; Wakita et al., 1994). The principal advantage of this model is that it produces preferential white matter lesions while sparing the gray matter and visual pathways, potentially due to a milder reduction in CBF. However, a period of chronic hypoperfusion is required before prominent white matter lesions appear (Krafft et al., 2012). Histologically, carotid artery occlusion-induced permanent blockade of the bilateral common carotid arteries results in a sizable drop in cortical blood flow leading to loss of cellularity, vacuolation of myelin and astroglial reactivity in major white matter structures, such as the optic nerve, corpus callosum, internal capsule and cognitive impairment (Hainsworth and Markus, 2008; Wakita et al., 1994). However, there is another model which involves progressive and slow common carotid artery occlusion using ameroid constrictors (Kitamura et al., 2012).

A study employed longitudinal two-photon imaging to characterize the effect of diabetic hyperglycemia on photothrombotic stroke induced alterations in microvascular blood flow dynamics in mice (Tennant and Brown, 2013). Diabetic animals following photothrombotic

stroke displays impaired recovery of sensory functions, reduced post-ischemic reorganization of sensory cortex, deficits in cortical plasticity and ischemic loss of dendritic spines (Reeson et al., 2016; Reeson et al., 2015; Sweetnam et al., 2012). A similar use of longitudinal two-photon imaging based assessment of stroke-induced changes in CBF and brain plasticity during diabetes may help in identifying the role of cerebral vasculature in diabetes-induced loss of cortical plasticity, aggravation of ischemic brain damage and a potential delay in recovery.

6.5 Other models of stroke

A subset of stroke patients are known to suffer from the lacunar subtype which is characterized by the presence of small infarcts in the gray matter of the subcortical area, or white matter or brainstem (Fisher, 1982; Sudlow and Warlow, 1997). Moreover, lacunar stroke is a widespread form of ischemic stroke observed in subjects suffering from T2D (Shah et al., 2008). A group has reported an ouabain-induced model of deep-seated lacunar stroke in rats (Janowski et al., 2008). The animal models enumerated in various sections above also generate small subcortical lesions. However, in the context of such a sizable presence of the disease condition, an animal model mimicking the clinical condition of small vessel pathology is still required. Application of such a model holds great promise in terms of furthering the understanding of pathogenic mechanisms of lacunar stroke involved in diabetic aggravation of ischemic brain injury by bridging the gap between complexities of clinical condition of subjects suffering from the disease and reflection of the same in animal models.

7. Points of consideration for selecting diabetic stroke model

Diabetes enhances the risk of stroke (Kissela and Air, 2006; Kothari et al., 2002). However, the animal models being currently employed to study diabetes-related stroke aggravation fail to provide an all-encompassing model to study different pathogenic mechanisms simultaneously. Therefore, in order to ensure clinical relevance of the efficacy data generated using the animal models described above (Table 2), it is important that careful consideration be given to the factors associated with diabetic stroke and the methods by which diabetes potentiates stroke injury. Secondly, animal model selection also should consider target sub-population of diabetics (ischemic stroke, hemorrhagic stroke, cardiac arrest) intended to be treated with drug(s) under assessment. Thirdly, as most of the diabetic patients suffering from stroke are advanced in age and suffer from a range of other comorbidities such as hypertension, it may be appropriate to incorporate such conditions into animal models. Moreover, experimental infarcts produced by the animal models must be reproducible and surgical methods involved in generating the animal models should be minimally invasive. It is also important to monitor physiological parameters as variation in these might affect outcome measures (Durukan and Tatlisumak, 2007). STAIR consortium recommends evaluating functional outcomes in preclinical drug testing (Stroke Therapy Academic Industry, 1999). There is a battery of behavioral outcome measures available to assess cerebral ischemia-induced functional impairment in laboratory animals (Babcock et al., 1993; Corbett and Nurse, 1998; Hunter et al., 1998; Kuroiwa et al., 1991; Wang and Corbett, 1990). Sweetnam et al. have shown that diabetes impairs cortical plasticity and

functional outcome following ischemic stroke (Sweetnam et al., 2012). Therefore, evaluating behavioral outcome measures, along with histopathological outcomes, may be important while testing potential neuroprotective drugs against increased ischemic damage in diabetes.

Animal studies have largely avoided including diabetic group treated with anti-hyperglycemic drug therapy while evaluating effect of diabetes on stroke outcomes. Inclusion of such group is important as a diabetic stroke patient typically receives anti-hyperglycemic therapy during, at least, early phase post-stroke in a clinical setting. Therefore, in order to ascertain the true clinical potential of novel therapeutic strategies in animal models, it is important to include treated-diabetic group while evaluating the efficacy of neuroprotective drugs.

8. Summary and Future Directions

Studies using various animal models of cerebral ischemia and stroke have highlighted the potential of a number of therapeutic strategies to treat diabetes-induced exacerbation of ischemic brain damage (El-Sahar et al., 2015; Suda et al., 2015; Zhao and Hu, 2014; Zhao et al., 2015a). Animal studies may benefit from evaluating the neuroprotective effect of test drugs in presence of anti-hyperglycemic therapy. Further, given the complex nature of metabolic changes during diabetes that influences brain physiology, categorical efficacy data that may facilitate clinical development of the above approaches are mostly missing (Biessels and Reijmer, 2014; Mansur et al., 2014; Palacio et al., 2014; Paquereau et al., 2014; Shindo and Tomimoto, 2014). Furthermore, the nature of temporal metabolic changes associated with pathological progression of diabetes may differently affect the nature and the extent of cerebral ischemic damage (Bryan et al., 2014; Nakayama et al., 2015; Zhang et al., 2014b). Thus, the duration of diabetes may affect efficacy of therapeutic strategies for treating ischemic brain injury. Moreover, a large subset of patients suffering from diabetes is old (McDonald et al., 2015) and aging is noted to substantially alter the pathophysiological progression of diabetes (Abbatecola et al., 2015). In addition, coexistence of other comorbidities like hypertension and hyperlipidemia may also contribute towards the aggravation of ischemic brain damage among diabetics (Alonso-Moran et al., 2015; Cao et al., 2015; Grabowski et al., 1988; Herz et al., 2014; Herz et al., 2015; Zhao et al., 2015b). Therefore, factors affecting pathophysiology of diabetes like aging and other comorbidities should be considered while selecting cerebral ischemia models for diabetes research. Further, studying correlation between data of efficacy of a therapeutic approach obtained from different animal models representing separate aspects of disease mechanisms may help us understand the nature and extent of efficacy of the approach on brain damage during stroke among diabetics. This may help us in identifying key pathophysiological mechanisms of diabetic enhancement of brain injury during stroke that might hold promise to treat the disease situation.

9. Conclusion

In the present article, we have identified animal models to study ischemic brain injury during diabetes. A careful application of the recommendations of the STAIR criteria to a judiciously selected set of animal models and their use to study the effect of various aspects

of diabetic manifestations on brain during stroke / cerebral ischemia may ensure generation of more clinically relevant data. Disparate animal models mimic different pathological manifestations of diabetes and the simultaneous presence of these aspects may differentially influence the diabetes-related heightening of ischemic brain damage. Therefore, selection of an appropriate animal model is critical in identifying the clinical potential of new therapeutic strategies for stroke among diabetic subjects. Moreover, efficacy research integrating different models of diabetes representing various elements of diabetic pathophysiology may help better evaluate the therapeutic potential of novel drugs to lower stroke / cerebral ischemia damage in diabetics.

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Abbreviations

Ay

Yellow obese gene

BB rats

BioBreeding rats

BCCA

Bilateral common carotid artery

CA

Cornus ammonis

CBF

Cerebral blood flow

CXCR4

C-X-C chemokine receptor type 4

db/db mouse

diabetic dyslipidemic mouse

FCI

Focal cerebral ischemia

GCI

Global cerebral ischemia

ICH

Intra-cerebral hemorrhage

KK mouse

Kuo Kondo mouse

Lep

Leptin

Lepr

Leptin receptor

LEW.1AR1/Ztm-iddm rats

Type 1 diabetes mellitus rat model which arose through a spontaneous mutation in a congenic Lewis rat strain with a defined MHC haplotype

MCA

Middle cerebral artery

MCAO

Middle cerebral artery occlusion

NOD mice

Non-obese diabetic mice

ob/ob mouse

Leptin-deficient obese mouse

OLETF rats

Otsuka long evans tokushima fatty rats

SAH

Sub-arachnoid hemorrhage

STAIR

Stroke therapy academic industry roundtable

tPA

Tissue plasminogen activator

4-VO

4-Vessel occlusion

2-VO

2-Vessel occlusion

WBN/Kob rats

Wistar Bonn/Kobori rats

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Highlights

- Cerebral ischemia produces profound injury in diabetics.
- Diabetes is an important comorbidity of cerebral ischemia.
- It is important to test new therapies of cerebral ischemia in models of diabetes.
- Available models of diabetes and cerebral ischemia are described.

Table 1

Proportion of stroke models used in 63 diabetes experiments

The table shows the frequency of use of different stroke models in diabetes research. The search for literature was carried out on February 2, 2017 using PubMed using ‘models of cerebral ischemia and diabetes’, ‘hemorrhage and brain and diabetes and animal’, ‘subarachnoid hemorrhage and diabetes and animal’, and ‘cardiac arrest and diabetes and animal’ keywords.

Animal model	Percentage of all articles found	Model subtype	Percentage of respective model
Global cerebral ischemia	25 %	Two-vessel occlusion model of forebrain ischemia	75 %
		Four-vessel occlusion model of forebrain ischemia	19 %
		Cardiac arrest and resuscitation	6 %
Focal cerebral ischemia	68 %	Transcranial surgical MCAO	8 %
		Endovascular MCAO	82 %
		Thromboembolic MCAO	11 %
Cerebral hemorrhage	4 %	Subarachnoid hemorrhage	33 %
		Intracerebral hemorrhage	67 %
White matter stroke	3 %	Bilateral carotid artery stenosis	100 %

Table 2

Summary of use of stroke models in diabetes research

The table shows the pathophysiology mimicked, clinical relevance and notes regarding different animal models used in diabetic stroke research.

Models	Pathology	Clinical relevance	Notes	References
Chemically induced diabetes	Hyperglycemia induced ischemic brain injury in T1D	Used for testing the effect of variations in glycemic status on stroke outcome	Technically simple, cost effective and established method of studying the effect of diabetic hyperglycemia on ischemic brain injury.	(Britton et al., 2003; Li et al., 2004; Rizk et al., 2007; Rizk et al., 2005; Rizk et al., 2006)
BB rats	Brain injury and neuroinflammatory changes during T1D	Used to study genetics of T1D, efficacy of interventions and tolerance of islet transplantation	Used to model diabetic metabolic changes in ischemic brain in diabetes	(Sutherland et al., 1992)
Akita mice	Infarct size, edema, inflammation, and cell death during T1D	Serves as an alternate to streptozotocin-treated mice in transplantation studies and as a model of T1D macrovascular disease	Recently used to study epigenetic and neurovascular mechanism of T1D-induced exacerbation of ischemic brain injury	(Kalani et al., 2015)
$Lep^{ob/ob}$ / $Lep^{d/b}$ mice	Larger infarct volumes and impaired recovery linked with greater infiltration of macrophages with T2D	Useful for testing treatments to improve insulin resistance	Employed to study inflammatory mechanisms of diabetic exaggeration of ischemic brain injury	(Kumari et al., 2011; Kumari et al., 2010)
KK/KK- A^Y mice	Ischemic infarct and neurological deficit in T2D	Useful to test the efficacy of drugs on T2D	Used in an efficacy study involving diabetic increase in ischemic brain damage	(Iwanami et al., 2010)
Zucker Diabetic Fatty rat	Infarct size, edema, neurological function deficit, soluble intercellular cell adhesion molecules, and cerebral expression of neutrophil-endothelial inflammatory genes in T2D	This model mimics development of diabetes in humans	Recently has been used to study inflammatory mechanisms of T2D induced ischemic brain damage	(Ritter et al., 2011)
Goto-Kakizaki rat	Neurobehavioral outcomes, infarction, hemorrhage, and edema in T2D	This animal type models secondary complications of diabetes such as retinopathy and neuropathy	Represents hemorrhagic transformation and neurological deficit after MCAO in diabetes	(Hafez et al., 2015)
OLETF rats	Increased apoptosis and ischemic lesions in T2D	Employed to test treatments improving insulin resistance	Proposed as a model of diabetic enhancement of venous ischemia	(Wajima et al., 2010)