Experimental Neurology 292 (2017) 63–79

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Review Article

Diabetic aggravation of stroke and animal models

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ARTICLE INFO

Article history:
Received 2 September 2016
Received in revised form 3 February 2017
Accepted 3 March 2017
Available online 6 March 2017

Keywords:
Global cerebral ischemia
Focal cerebral ischemia
Stroke
Translational research
Preclinical models
Hemorrhage
White matter damage

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.

Contents

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, subarachnoid 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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http://dx.doi.org/10.1016/j.expneurol.2017.03.004
0014-4886/

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-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 world-wide, 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 >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, G, 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 wide-spread 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