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Review

A review on animal models of stroke: An update

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ABSTRACT

Stroke is one of the major healthcare challenges prevailing across the globe due to its significant rate of mortality and morbidity. Stroke is multifactorial in nature and involves several cellular and molecular signaling cascades that make the pathogenesis complex and treatment difficult. For a deeper understanding of the diverse pathological mechanisms and molecular & cellular cascades during stroke, animal modeling serves as a reliable and an effective tool. This also helps to develop and critically analyse various neuroprotective strategies for the mitigation of this devastating disease. Animal modeling for stroke has been revolutionized with the development of newer and more relevant models or approaches that mimic the clinical setting of stroke to a greater extent. This review analyses experimental models of stroke (ischemic and hemorrhagic) and their reliability in stroke situation. Besides this, the review also stresses upon the use of various preclinical models to understand the pathophysiological mechanisms that operate during stroke and to elucidate new, safe and effective neuroprotective agents to combat this life threatening healthcare concern.

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1. Introduction

Stroke is a severe condition of medical emergency with a very narrow treatment window. It is one of the prime healthcare concerns in both the developing and developed nations contributing to healthcare costs in a significant amount. It is associated with a very high rate of mortality and the patients who survive the initial injury usually suffer from motor impairments which may be regarded as a complete or partial loss of muscle function, mobility and control (Langhorne et al., 2009).

The human central nervous system has a vasculature which has a unique feature of preserving blood flow to the critical brain structures. The internal carotid arteries supply blood to the cerebral hemispheres. The Basilar arteries supply into the cortex through the two converging vertebral arteries. The carotid and basilar artery system interconnections occur through Circle of Willis which is responsible for reversal of flow and cross filling of deep brain structures (del Zoppo and Hallenbeck, 2000). The protective arrangements are effective only if there is no vascular injury within the arterial blood supply. Obstruction in the blood supply or injury in the cerebral blood vessels leads to the origin of cerebrovascular diseases (CVD). Obstruction of blood flow may occur due to the formation of an atherosclerotic plaque or due to thrombus formation which results from activation of clotting cascade following injury to the vessel wall. Besides thrombus formation, blood flow disruption and consecutive infarcts can result from emboli which may result from vascular lesions located proximally or distally to the cerebral blood vessels (Donnan et al., 2008).

Stroke is a form of CVD which affects blood supply to the brain and was initially referred to as apoplexy (Nilsen, 2010). WHO defines stroke as '*rapidly developed signs of focal (or global) disturbance of cerebral function lasting longer than 24 h (unless interrupted by death), with no apparent nonvascular cause*' (Aho et al., 1980). Stroke in general, refers to a disturbance in the functioning of the brain caused due to interruption in blood supply which may be either due to blockage or rupturing of the blood vessel. This damage is mostly permanent and irreversible. To function properly, neurons and associated cells in the brain require a regular supply of blood, oxygen and glucose. An impairment in the supply of these components results in a temporary brain damage. Permanent damage to the brain depends on the severity and duration of the impaired blood and oxygen supply. Very severe damage may lead to neuronal death subsequently causing an impairment in the normal physiology and functioning of the organs associated with the damaged area of the brain (Lipton, 1999).

1.1. Epidemiology

Stroke, being the second leading cause of death (Mozaffarian et al., 2015) and third leading cause of disability (Murray et al., 2012), is considered as major health problem worldwide. The percentage of deaths occurring due to stroke in developing countries is about 87% (Lopez et al., 2006). As per WHO, stroke is responsible for second highest number of deaths in people aged more than 60 years, and fifth highest number of deaths in people aged 15–59 years (Mackay and Mensah, 2004). Millions of people die every year from stroke globally (Alwan, 2011; Feigin et al., 2015). Epidemiological studies of Western European countries suggest that stroke is more common in men than in women, however the severity and fatality of stroke is higher in women as compared to men (Appelros et al., 2009). Depression and memory loss are the major post stroke complications (Langhorne et al., 2000) and approximately 33 million people are currently living with stroke induced disability (Corbyn, 2014).

1.2. Risk factors for stroke

The origin of stroke is multifactorial in nature. Numerous risk factors of stroke have been identified and been targeted in prevention of stroke. These can be classified on the basis of their potential for modification (modifiable, non-modifiable or potentially modifiable) and on Lifestyle induced conditions or diseased conditions (Fig. 1). Age, sex, ethnicity, genetic makeup and low birth weight constitute the non-modifiable risk factors. Factors like diabetes, chronic hypertension, hypercholesterolemia, smoking, previous history of heart disease like atrial fibrillation, ploycythemia, carotid artery stenosis and other conditions like poor dietary intake, obesity and post menopausal hormone therapy are considered as modifiable risk factors. Metabolic syndrome, alcohol abuse, migraine headache, hypercoagulability and inflammation constitute the potentially modifiable risk factors for stroke (Sacco et al., 1997). Hypertension is the major risk factor in both the types of strokes as the increased pressure damages the arterial walls making them more vulnerable to narrowing (atherosclerosis) or rupturing. Mild elevations in blood pressure can be seen with increased risk of stroke and can be modified with drug therapy or lifestyle modification. High cholesterol levels are also thought to pose a risk for stroke but the exact mechanism for direct involvement is not known. However, hypercholesterolemia increases the risk of cardiovascular diseases like atherosclerosis which is a major risk factor for stroke (Shigematsu et al., 2015).

Carotid bruit is also a risk factor for stroke. Bruit is a noise made by the turbulent flow of the blood in the larger arteries like carotid which can be heard only with the stethoscope. Bruit occurs mainly because of narrowing of the vessels due to atherosclerosis (Rich, 2015).

2. Types of stroke

Stroke can be classified into two basic types, namely ischemic stroke and hemorrhagic stroke (Fig. 2).

2.1. Ischemic stroke

As per American Heart Association/American Stroke Association, ischemic strokes account for 80–87% of all cases (Mozaffarian et al., 2015; Sudlow and Warlow, 1997). This type of stroke occurs due to an obstruction in blood flow and thus oxygen supply to the brain. The underlying condition for the obstruction of blood flow to the brain is atherosclerosis wherein fatty deposits develop in the inner vessel walls. It can result in the formation of two types of clots namely thrombus and embolus. On this basis, ischemic strokes can be sub classified into Thrombotic Ischemic Stroke and Embolic Ischemic Stroke (Adams et al., 1993).

(a) Thrombotic Ischemic Stroke: In this type of Ischemic stroke, a thrombus clogs the blood vessel resulting in obstruction of blood flow to the brain. The narrowing of blood vessel creates a low flow state which is referred to as distal field ischemia. The consequent lack of oxygen leads to the death of brain tissue