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REVIEW ARTICLE

Overview of Advances in the Pathophysiology and Treatment of Stroke: A New Plan for Stroke Treatment

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Abstract: Despite many advances in the treatment of stroke, this disease still causes great morbidity and mortality. For this purpose, different kinds of studies have been conducted based on different mechanisms. The research findings highlight the role of remote ischemic preconditioning, microRNAs, neurogenesis, inflammation, and oxidative stress. Nearly a quarter of patients with ischemic stroke will experience a recurrent stroke. It means not just immediate intervention, but also long term intervention is necessary to alleviate stroke patients. Therefore, it is mandatory to predict unwanted events and implement a thoughtful treatment, especially targeting high-risk patients with a high rate of mortality and morbidity. In this review, new advances in animal models have been proposed and overall, it is concluded that stroke patients may greatly benefit from multidisciplinary solutions and more studies are being conducted for timely implementing the best therapy.

Keywords: Stroke, Remote ischemic conditioning, MicroRNA, Neurogenesis, Inflammation, Pathophysiology.

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1. INTRODUCTION

Despite many advances in the treatment of stroke and its sequels [1, 2], stroke is still the main disease that has the greatest burden of mortality and morbidity [3, 4]. It is obvious that by increasing the global population of people who suffer ischemic episodes, the more people would suffer from this severe disease [5 - 7]. People who are older than 65 years of age are the population that is at great risk of morbidity and mortality, and also overall, the incidence of stroke has been increased [8 - 10]. However, it would not be surprising to see this disease in younger people. Considering the global burden of the disease, many studies have been conducted to reduce the morbidity and mortality from this serious disease [11, 12]. New strategies and treatments have been conducted for the prevention, immediate and long-term treatment of stroke [13 - 15]. Here, new advances in managing this disease and its complications, especially in animal models have been discussed.

2. DISCUSSION

2.1. Remote Ischemic Conditioning as a Protective Treatment

The protective role of oxygen deprivation was known in 1939 [16]. However, in 80s, new experiments were performed

to investigate this protective phenomenon [17]. Many studies were performed to investigate the protective effect of Remote Ischemic preconditioning (RIC). The protective role of RIC is limited only to the brain, but also RIC has a protective role in other organs such as lung, liver, and skin [18]. In addition, many other diseases such as renal disease will benefit from RIC [19]. For sure, RIC would activate adaptive mechanisms in neurons, but the exact mechanism for its protective role has not fully understood. However, hypoxia-inducible factor 1 recently has been proposed to be necessary for the protective role of RIC [20]. Macrophage activation has also been considered as a key event in the progression of reperfusion injury which is known as the source of extracellular Reactive Oxygen Species (ROS) [21]. Meanwhile, there is a window period that the ischemic myocardia can be secured before necrosis established. In this regard, activation of neutrophils, adhesion molecules and cytokine release is necessary for the induction of necrosis, but RIC yet has not been shown to influence these mechanisms. RIC is not just useful for stroke as the consequence of atheroma plaque but also in different conditions, it is an effective strategy. RIC treatment prevents stroke in intracranial arterial stenosis [22], focal ischemia [23] and after subarachnoid hemorrhage [24]. RIC can also be induced by chronic peripheral hypoperfusion, not just by occlusion of vessels [25]. Stroke as the side-effect of cardiovascular surgeries and intervention of palliative care in the cardiovascular system can be alleviated by RIC [26 - 28].

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2.2. Role of microRNAs in Determining the Outcome of Stroke

MicroRNAs are small, non-coding RNAs that, in recent years, have got much attention for the treatment of stroke [29 - 35]. MicroRNAs have a role in many neuronal processes such as development, differentiation, synaptic plasticity [36], apoptosis [37] and neurodegeneration [38]. It has been shown that microRNAs can influence the outcome of stroke. Some microRNAs improve and some microRNAs deteriorate the process of stroke [39]. MicroRNAs in the pathogenesis of atheroma plaque, stroke, and its complications have a more validated role compared to RIC. They are present in atherosclerosis, hyperlipidemia, hypertension and plaque rupture [40]. Following ischemia, a profound change in microRNA transcriptome occurs in the myocardium [41 - 43]. Apart from other microRNAs that are released after ischemia, two microRNAs are pathophysiologically active in the window period. These are microRNA-15a and microRNA 497. These two microRNAs have a negative role in the pathophysiology of stroke. They impair the normal defense mechanism that begins after ischemia present inside the cells. MicroRNA-15a inhibits expression of Bcl-2 [44] and microRNA 497 interferes with the normal function of Bcl-2 [45] that has an antiapoptotic role. Further studies suggest that reduction of the production of such microRNAs protects the blood-brain barrier (BBB). RIC treatment has been shown to cause up-regulation of the member of microRNA 200 family (200 a, 200 b and 429) [46]. About the effectiveness of microRNA directed therapy for the alleviation of stroke, further studies should be done to validate the specific treatment. However, microRNA-targeted therapy that promotes cell survival can be considered in this regard [47]. In a recent study, microRNA, Let7f has been successfully used for neuroprotection in ischemic stroke model [48]. MicroRNA 124a in the subventricular zone [49] and microRNA 17-92 [50] have also been successfully used in the stroke model through increased survival of ischemic cells. MicroRNA 107 contributes to post-stroke angiogenesis [31]. Targeting other cells such as oligodendrocytes that may help better healing of ischemic region is also a useful treatment. MicroRNA 146a promotes oligodendrocytes in the ischemic region [51].

2.3. Neurogenesis, Angiogenesis, and Synaptogenesis

The generation of new neurons after birth in certain brain regions is called Neurogenesis [52]. In mammals, in some brain areas, continuous neuron production is well documented: the Subventricular Zone of the lateral ventricle (SVZ) and the dentate gyrus of the hippocampus [53]. From the SVZ, neuronal progenitors migrate along the Rostral Migratory Stream (RMS) into the Olfactory Bulb (OB), where they differentiate into granule and periglomerular neurons [54 - 56]. In contrast, glial progenitor cells migrate radially into neighboring brain structures such as the striatum, corpus callosum, and neocortex [57, 58]. The migration of new neurons for neurogenesis niche specifically the subventricular zone, may improve the outcome of stroke [59]. In the recent two decades, many studies have been conducted to investigate the effectiveness of this new phenomena (Neurogenesis) in brain diseases such as stroke and these studies suggest that this

self-impair capacity alone fails to reconstruct the infarcted area after stroke and there should be some regulators for healing of the infarcted area that increases the efficacy of newly generated neurons [60, 61]. Studies in this regard suggest that some agents such as Epithelial Growth Factor and basic Fibroblast Growth Factor (EGF/bFGF) and Transforming Growth Factor α (TGF α) may increase the efficacy of recruited neurons for reduction of infarct volume [61 - 63]. It should be remembered that the recruited new neurons themselves may be sufficient for exerting such a healing effect. Neurogenesis in other brain areas such as forebrain [64], cortical areas [65], hippocampus [66] and striatum [67] has been observed following a stroke. This phenomenon encouraged new studies that are directed at knowing the exact mechanism of this recruitment and also proposing effective treatment on this basis. Later studies proposed that the application of some drugs by improving neurogenesis improves the outcome of stroke. Drugs such as valproic acid [68], erythropoietin [69], statins [70], sildenafil [71], transforming growth factor α [72], retinoic acid [73], N-methyl-D-aspartate mediated therapy [74], nitric oxide donor [75], omega-3 polyunsaturated fatty acids [76], cerebrolysin [77], administration of CD34⁺, fluoxetine [66] and exercise [78] are included.

2.4. Inflammation Process

Inflammation is a complex process that encompasses the accumulation of immune cells in a certain region [79]. During this complex process, certain receptors will appear in immune cells and also certain mediators will be released [80]. It has been shown that after stroke, certain inflammatory processes will occur in the ischemic region [81]. Various kinds of immune cells recruited to the ischemic region including Microglial cells, neutrophils, macrophages/monocytes and T-cells [80]. Modulation of the immune system will decrease the size of infarct [21, 82, 83]. Post-ischemic inflammation leads to dysfunction of the blood-brain barrier, cerebral edema, and neuronal cell death [84]. The important question in this regard is the old concept about the brain that has been thought to be an immune-privileged organ. Microglial cells are thought to be the immune modulator during the stroke. The number of microglial cells increases after stroke in the infarcted area [85]. In fact, microglial cells can play two distinct roles: protective effect and destructive effect. The protective role is the result of the production of neurotrophic substances Brain-derived Neurotrophic Factor (BDNF), insulin-like growth factor I (IGF-I), and several other growth factors. The destructive effects mainly mediated by releasing several pro-inflammatory cytokines such as TNF- α , interleukin-1 β (IL-1 β), and IL-6, as well as other potential cytotoxic molecules including Nitric Oxide (NO), ROS, and prostanooids [86]. Microglial cells by the production of proinflammatory cytokines can trigger the emergence of adhesion molecules and, therefore recruitment of inflammatory cells to penumbras. In this sense, a new therapy has been proposed for the reduction of inflammation in the infarcted area [87, 88]. Based on this observation, inflammatory mediators and cells can be used to assess the outcome of stroke. In one study, IL-6 has been used to assess the severity of stroke [89] and Toll-like receptor 4 has been considered as the marker that is associated with severe stroke

[90]. Regulatory T cells have a protective role during the stroke [91]. Metalloproteinase, based on its anti-inflammatory properties, has been proposed for the treatment of stroke [92].

2.5. Oxidative Stress (OS)

The balance of oxidative stress is a detrimental factor for normal body function, including the brain [93]. It has been shown that during acute ischemia, considerable oxidative stress is present in the region of ischemia [94]. In this sense, oxidative stress during ischemia is the cause of great mortality [94]. It is proposed that during the ischemic period, rapid reperfusion causes the second period of reactive oxygen species (ROS) generation that causes more damages, such as disruption of the Blood-brain Barrier (BBB) [53, 95]. The resultant ROS generation will affect the outcome of stroke. ROS causes autophagy, apoptosis, and necrosis [96, 97]. The beneficial effects of antioxidant therapy are evolved from animal studies. It has been shown that vitamin C and E therapy along with other antioxidant agents such as NADPH-oxidase and Flavanol, will improve the outcome of stroke [98 - 100]. Moreover, Resveratrol, Apelin, Melatonin, and Minocycline have been successfully used for alleviation of stroke [101 - 104].

CONCLUSION

Stroke is a serious disease that causes many disabilities and mortalities. Many scientists are looking for new strategies to control the diseases' concerns. Here, the different progress in managing stroke was introduced. Some were applicable in clinical practices and some of them are not applicable in clinical practices. This progress introduces new horizons for the treatment of stroke and suggests that, for treatment of stroke, application of more than one strategy will protect more effectively the victims of stroke.

LIST OF ABBREVIATIONS

RIC	= Remote Ischemic Preconditioning
ROS	= Reactive Oxygen Species
Bcl	= B-cell lymphoma-extra-large
SVZ	= Subventricular Zone of the lateral ventricle
OB	= Olfactory Bulb
RMS	= Rostral Migratory Stream
TGFα	= Transforming Growth Factor α
EGF/bFGF	= Epithelial Growth Factor and basic Fibroblast Growth Factor (EGF/bFGF)
BDNF	= Brain-derived Neurotrophic Factor
IGF-I	= Insulin-like Growth Factor I
IL	= Interleukin
NO	= Nitric Oxide
BBB	= Blood-brain Barrier

AUTHORS' CONTRIBUTIONS

This work has been completed in collaboration with the two authors. Author HF has been provided the title and has been collected the relevant articles and has been written the first draft of the manuscript with the help of Author MK.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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