REVIEW ARTICLE

Neuroregeneration, neurodegeneration and brain recovery following ischaemic stroke: a comparative review of animal models and humans

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Abstract

Stroke is a leading cause of healthcare burden in the aging population with a rapidly rising prevalence worldwide. Ischaemic strokes account for 85% of the strokes. The key to recovery of brain functions following an ischaemic stroke depends on two arms: 1) restoration of lost or damaged neurones and, 2) survival of neurones that were not killed by the injury. Hence, the recovery could be hastened by promoting neuroregeneration and preventing neurodegeneration. During the last five decades, animal models showed promising results in the field of neuroregeneration, which was long believed to be impossible. Furthermore, animal studies with stroke lead to the discovery of the novel concepts of epigenetic inhibition in nerve growth, upregulation of apoptotic genes, neuroinflammation and metabolic dysregulation which contributed to neurodegeneration. However, it is debatable if these findings can be replicated in human brains, in order to develop potential therapeutic strategies.

Keywords

stroke, nerve regeneration, nerve degeneration, neurogenesis

Main Article

Stroke is defined as an acute brain insult due to a vascular event leading to permanent injury to neurones and functional compromise [1]. Strokes are caused by inadequate blood supply to the brain to meet its metabolic demands. They can be classified into two major sub groups based on the pathophysiology: ischaemic and haemorrhagic. Ischaemic strokes occur usually secondary to occlusion of a cerebral blood vessel [1]. Ischaemic strokes are by far the commonest type worldwide accounting for 85% of the strokes [1]. The Global Burden of Disease study concluded that ischaemic strokes account for 2 690 200 deaths in the world in 2016 [2]. The incidence of stroke in Asia is 116 to 483 per 100 000 per year [3].

Mechanisms of recovery from ischaemic stroke

The key to recovery of function following a stroke depend on two arms: 1) restoration of lost or damaged neurones and, 2.) survival of neurones that were killed by the injury. The mechanism of restoration of the lost or damaged neurones is by means of repair and regeneration. The repair of damaged long axons within the central nervous system is markedly limited, particularly

due to the active inhibition of axonal regrowth by the glial cells [4]. Conversely, the belief of inability of neurones to regenerate was challenged in recent studies.

Neuroregeneration

Altman in 1962 first described the neurogenesis in adult mammalian brain [5]. In 1998, Eriksson and colleagues found that the neurogenesis happens in the dentate gyrus of the adult human hippocampus [6]. Adult hippocampal neurogenesis declines with aging in rodents [7] and non-human primates [8]. There are striking differences of neurogenesis between humans and animals. Neuronal migration from subventricular zone to olfactory bulb along the rostral migratory system could only be demonstrated in rodent [9, 10] and non-human primate [11, 12] studies. Whereas, unique features like striatal neurogenesis was not demonstrated in animal studies [13, 14]. Likewise, there is conflicting evidence whether neurogenesis happens in the normal adult brains [15-18]. Using immunofluorescence staining, Sorrells and colleagues concluded that neurogenesis in humans rapidly declines from 7 to 13 years of age and it is almost non-existent in the adult age [19]. Despite adapting a fairly similar methodology, Boldrini and colleagues found that the neurogenesis persists in adult human brain even until the eighth decade of life, even though the quiescent neural stem cell population, neural plasticity and angiogenesis declines with aging process [20]. The contrasting evidence by these two landmark studies proves that understanding of the mechanism of adult neurogenesis is far from clear.

Similarly, the mechanism of neuroregeneration following ischaemic stroke is poorly understood. A few studies investigated the patterns of neuroregeneration following a stroke. Radiocarbon-14 dating studies failed to show neuroregeneration in forebrain following stroke [21], whereas immunocytological studies demonstrated a possible neurogenesis with migratory phenotype [22-24]. Few in vitro and in vivo studies elicited that the neurogenesis is co-regulated with angiogenesis [25-28]. An age associated decline in both angiogenesis and neuronal plasticity was found in a human study [20]. However, correlations of neuroregeneration and angiogenesis in humans are not reported.

Neurodegeneration

Ischaemic damage to the brain initiates a cascade of events which leads to death of partially injured neurones leading to neurodegeneration. Transcriptomic analyses of ischaemic penumbra of rats provided insight into temporal relationship of differential expression of genes responsible for metabolic, inflammatory and immunological pathways in post-ischaemic neurodegeneration [29]. Subsequent animal studies with stroke lead to the discovery of the novel concepts of epigenetic inhibition of axonal sprouting [30], extensive upregulation of apoptotic genes [29], neuroinflammation [31] and metabolic dysregulation [32]. However, genes which prevent inflammation [33,

34] and oxidative stress [35] after ischaemic stroke were also discovered. Nevertheless, controversial results against the apoptosis and gene fusion following stroke were found in a human study [21].

Conclusions

Nerve regeneration and degeneration may play a critical role in the recovery of stroke. However, we cannot ascribe the results of neuroregeneration and neurodegeneration found in animal models directly to humans. Human studies are scarce due to lack of access to tissues and technical problems of tissue handling and sequencing. Therefore, there are ambiguities and gaps in knowledge of the dynamic balance between protective and damaging factors leading to post-ischaemic neuroregeneration and neurodegeneration in humans.

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Conflicts of Interests

The authors declare that there are no conflicts of interests.