A review of the effects of environmental enrichment on stroke in animal experimental models

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Abstract
The purpose of this article is to present the environmental enrichment (EE) method used to improve the functional recovery and change of brain plastic in animal experimental models of stroke. In animal experimental models of stroke, the environmental enrichment is effective in altering the morphological, biochemical and behavioral characteristics of the brain and thereby improving the functional outcomes.

In this review article, we address the effects of EE in achieving a functional recovery in animal experimental models of stroke, thus attempting to describe them in patients with stroke from both occupational and rehabilitation perspectives.

Key Words: Stroke, Environmental enrichment, Behavioral, Animal experimental models, Rehabilitation therapy

1. Introduction

Stroke is the third leading cause of death worldwide and it is also the major course of long-term disabilities in industrialized countries. Most of the surviving stroke patients achieve a substantial degree of spontaneous recovery, but they commonly have a persistent presence of sensorimotor and cognitive dysfunctions[1].
뇌졸중 동물 실험 모델에서 환경 강화 효과에 대한 종설


Ischemic stroke mainly occurs as a result of large-vessel atherosclerosis, embolisms, thrombosis and small-vessel occlusions. Some risk factors of stroke can be modified; these include high blood pressure, diabetes mellitus, smoking, alcohol abuse, diet or atrial fibrillation. But other risk factors, such as age, gender, race and genetic predisposition, cannot be modified[2].

A forced or robot-assisted training is effective in improving the degree of recovery of motor functions after stroke. To date, it has been proposed that the social and physical environment is associated with the improvement of recovery in patients with stroke[3-5].

Animal models of stroke are of great significance in not only examining the pathophysiologic mechanisms by which patients with stroke achieve a recovery of symptoms but also evaluating the efficacy of new therapeutic agents. Animal models of environmental enrichment (EE) are an experimental paradigm for conducting animal studies to examine the physical, social and intellectual activity and thereby to predict similar patterns in humans. Thus, experimental animals are subjected to physical exercise (e.g., wheel running) and exposure to a variety of passive visual stimuli (e.g., changes in the color of the background and object)[6].

In this article, we address the effects of EE in achieving a functional recovery in animal experimental models of stroke, thus attempting to describe them in patients with stroke from both occupational and rehabilitation therapy.

2. Environmental enrichment

The enriched environment(EE) is referred to as a group housing of healthy rats in a large cage with toys, for which changes are made daily in such a manner as to increase the neuronal plasticity and thereby to achieve a recovery of the experimental stroke in them[1]. In this experimental model, the training has a positive effect in achieving a functional recovery after brain damage. Such physical exercises as wheel running have been reported to stimulate the cell division as well as net neuronal survival in rats[7]. This has led to the speculation that the beneficial effects of EE might be totally or near totally based on the increased voluntary exercise. Thus, it can promote the activation, signaling and plasticity of neurons over the cerebral regions. This is followed by the activation of the somatosensory and visual cortex through the increased sensory stimulation due to the increased somatosensory and visual input[8].

It is known that intact rats become vulnerable to alterations in the morphological, biochemical and behavioral characteristics of the brain by exposure to EE. Moreover, the EE would be more effective on the behavior of rats; this would be notably effect on the learning and problem-solving activity. Furthermore, it has been known to be effective in improving the spatial memory and achieving a functional recovery[9-16]. With the accumulated experience of the EE, it has been shown to be effective in inducing numerous forms of brain plasticity and thereby improving the structure and function of brain[13,17]. Experimental studies have also shown that the EE caused substantial changes in the brain structure in rats; these changes include increases in the brain weight, the thickness of cerebral cortex, the size of neuronal body, the number and length of dendrites, dendritic arborization, the number and density of dendritic spines, the number of synapses, capillary diameter and the number of glial cells. Thus, the EE is mainly involved in the alteration of brain plasticity[6,18-22].

Later studies have shown that the EE had more specific effects in altering various types of neurotransmitters; these include increases in cerebral levels of noradrenalin, the activity of acetylcholinesterase and levels of glutamate receptor subunits, GluR1, NR2A and NR2B, but not NR1, in the forebrain. In addition, the EE has also been reported to
be effective in inducing the up-regulation of neurotrophic factors, including GDNF, BDNF, NGF and NT-3, and altering the degree of the expression of various immediate early genes, including NGFI-A and Arc, in the hippocampus and cerebral cortex\[1,23-29]. These reports indicate that the EE triggers the expression of many genes that are involved in the neuronal plasticity, thus having a great effect on the behavior of rats, including the learning and memory, in an experimental setting.

2.1 Environmental enrichment and stroke

To date, the effects of EE have been studied the most commonly using rats and mice. But its beneficial effects have been well documented in other mammalian species such as gerbils, ground squirrels, cats and monkeys. This has established the effects of EE in various experimental conditions. But there is a variability in the effects of EE depending on the species, age and gender\[30-32]. Moreover, it has also been reported that the EE has positive effects on the recovery after various types of brain damage, including the hippocampal and cortical lesions\[33].

2.2 Effect of environmental enrichment in animal models of stroke

Animal models of stroke have shown that the EE increased the neural stem/progenitor cell pool and stimulated the neurogenesis in the adult subventricular zone at 5 weeks after inducing the cortical stroke\[34]. This is accompanied by the alterations in the density of dendritic spines in the pyramidal neurons that are located contralateral to the cortical infarct\[35]. The aging process occurs in association with the temporary dysregulation of cellular response to ischemia and poor functional recovery. It has been shown that there was improvement in the motor functions with the continuous use of EE after the onset of ischemia although it increased the mortality. Moreover, after a 2-week exposure to the EE, followed by a 2-week group housing of mice in standard cages, there was no further improvement in the motor functions. By contrast, after a 4-week exposure to the EE, there was improvement in the motor functions accompanied by a better maintenance of the neurologic recovery. Animal studies have also shown that the degree of the expression of immediate-early genes, such as nerve growth factor-induced gene A, was decreased at 2-3 weeks after the experimental animals achieved a recovery following the EE. This suggests that such genes are involved in the recovery process. Moreover, experimental studies have also shown that the EE was effective in the functional outcomes after the onset of stroke in mice. Furthermore, further genomic studies in this series have been conducted using the experimental procedures that have been performed for the EE\[1].

Following the onset of the permanent middle cerebral artery (MCA) occlusion using the EE in rats, there was a decrease in the degree of the expression of migration inhibitory factor (MIF) in the peri-infarct areas, which was accompanied by an increase in parvalbumin immunoreactive interneurons. This indicates not only that the MIF is part of a signaling network involved in the brain plasticity but also that it is also involved in the inhibition of the recovery of sensory and motor functions after the onset of stroke once its levels in the neurons or astrocytes are elevated. Thus, the MIF could contribute to promoting a recovery of the stroke as a potential therapeutic approach\[28].

It has previously been suggested that the temporary modulation of the astrocytic proliferation, followed by the scar formation, might be effective in achieving a functional recovery after the onset of stroke in aged rats\[33]. In addition, this is followed by the compensatory movement in the early phase of post-lesion period. Thus, the EE is involved in the functional improvement. The beneficial effects of EE are based on the increased motor activity that mainly
arise from the compensatory process[36]. It has also been reported that the EE is also effective in postoperatively improving the spatial memory deficits after the onset of other brain injuries such as traumatic brain injury and surgical hippocampal lesions. But it is less effective in improving the symptoms of focal cerebral ischemia[37,38].

The beneficial effects of EE in achieving a recovery of the symptoms after the onset of focal ischemia are not based on the decreased volume of infarct[35]. This indicates that the beneficial effects of EE are based on the increased plasticity of the cerebral areas that are adjacent to the lesions. In addition, it has also been reported that the EE is also effective in increasing the length and branching of dendrites in the contralateral cortex during the post–ischemic period when combined with the rehabilitative training[3,39]. Focal cortical ischemia is characterized by the increased neurogenesis in the ipsilateral dentate gyrus; this is comparable to the dentate gyrus of rats housed in standard cages, where there are no changes in the density of neurons, which can be explained by those in the morphology of neurons in an EE setting[20, 40].

To date, there are no extensive studies about the effects of EE on gene expression after the onset of focal ischemia. It has been proposed that there are same mechanisms by which the neuronal plasticity occurs in an EE setting in both healthy individuals and those with brain lesions. It is evident, however, that the ischemic events are mainly responsible for triggering the expression of genes that may be involved in the response to EE. This suggests that there is a variability in the expression of genes in an EE setting during the post–ischemic period. Thus, there may be delayed up-regulation of genes associated with the effects of EE in promoting the brain plasticity once down-regulated in response to the detrimental stimuli during the early phase after the onset of ischemia[1,32,41,42].

2.3 Effect of environmental enrichment in stroke patients

Clinical studies have shown that the cognitive cost of multitasking was decreased with the use of an adaptive version of NeuroRacer in a multitasking training mode in elderly people aged between 60 and 85 years as compared with both the active control group and the no-contact one. In addition, it has also been shown that the degree of efficacy of multitasking training was lower as compared with untrained 20-year-old subjects and it was sustained for six months. Furthermore, the multitasking training restored the neurological signs of cognitive control process due to aging, as demonstrated on electroencephalography. Thus, it was effective in increasing the sustained attention and working memory, accompanied by the increase in the midline frontal theta power, by which the effects of multitasking training in increasing the sustained attention are preserved six months later. This strongly indicates that the multitasking training is effective in promoting the plasticity of the prefrontal cognitive control system in the elderly, which has not been described in the literature according to our knowledge. From the same context, custom–designed video games are used to assess the degree of cognitive functions, to analyze the underlying mechanisms and to improve the cognitive functions in individuals at all ages[43].

3. Conclusions

As described here, the EE is effective in maintaining or increasing the independence and thereby improving the quality of life in individuals with neurological deficits with no respect to whether they present with brain damage or trauma. Such individuals deserve social, psychological and cognitive supports[44].

The EE may also be effective in improving the quality of life in patients with stroke, for which it is imperative that the patient–customized treatment
strategy be established from a rehabilitation perspective.

In animal models of stroke, the EE was effective in achieving a recovery of the sensorimotor functions after the onset of focal ischemia with no respect to the additional rehabilitation training[7,39,39,45].

The effects of rehabilitation training in achieving a functional recovery after the onset of brain injury are dependent on its timing and intensity. That is, earlier rehabilitation with or without higher intensity may lead to the aggravation of the brain damage [15]. The optimal timing of the EE combined with the rehabilitation training is 5 days after the onset of focal cerebral ischemia[39,46].

Thus, we propose that the EE combined with the rehabilitation training be performed in the field of occupational therapy and rehabilitation, both of which are based on the brain plasticity. This leads to the speculation that the external inputs are used to promote the cerebral reorganization. The treatment goals of occupational therapy are to restore the learning and working memory and to achieve a recovery of physical and cognitive functions. The rationale of rehabilitation therapy in the restoration of motor, sensory and cognitive functions is based on the efficient task-specific activities, for which the EE is effective in creating the optimal conditions for the successful outcomes of rehabilitation therapy.

Finally, there are several promising multi-modal approaches in the field of rehabilitation therapy, which are based on latest updates on neurophysiology and technological advances. Thus, considerable efforts have been made to restore the brain capacity and thereby to achieve a functional recovery in patients with stroke.

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