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ENVIRONMENTAL INFLUENCE ON RECOVERY AFTER BRAIN LESIONS – EXPERIMENTAL AND CLINICAL DATA

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One aim of rehabilitation after brain lesions should be to optimise the function of the remaining intact brain. Experimental studies on focal cerebral infarcts in the rat have demonstrated that postischemic environmental enrichment significantly improves functional outcome, increases dendrite branching and number of dendritic spines in the contralateral cortex, influences expression of many genes and modifies lesion-induced stem cell differentiation in the hippocampus. Furthermore, environmental factors can interact with specific interventions such as necrotic grafting and drug treatment, which underlines the importance of general stimulation and activation in rehabilitation after brain damage. Animal laboratories often provide an environment with little stimulation. This should be taken into account when evaluating the clinical relevance of animal studies on long-term functional outcome after brain lesions.

Key words: plasticity, brain infarcts, functional outcome, transplantation, stem cell differentiation, dendritic spines

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INTRODUCTION

Most surviving stroke and trauma patients improve to some extent with time. Compared to the intense research on how to rescue neurons in the acute stage, surprisingly little clinical and experimental research has been directed towards the question of why a certain degree of functional recovery is possible despite permanent tissue damage. There is increasing evidence, however, that functional improvement after permanent brain lesions is related to lesion-induced plasticity in the intact brain tissue (1–7). An important question is to what extent postischemic events can influence lesion-induced plasticity. This review will deal with the influence of postischemic environmental factors – alone or in combination with specific therapeutic interventions – after experimental focal brain infarction, as well as its possible clinical implications.

ENVIRONMENTAL EFFECTS ON THE INTACT AND LESIONED BRAIN

Many studies have shown that housing intact animals in an enriched environment, i.e. in larger cages with access to various activities, significantly alters behaviour, brain morphology and biochemistry (8–11). Likewise, postischemic housing in an enriched environment can influence outcome after focal brain infarct induced by proximal or distal ligation of the middle cerebral artery (12-14), even when the transfer to an enriched environment is delayed for 15 days after the arterial occlusion (15).

ENVIRONMENTAL EFFECTS ON POSTISCHEMIC GENE EXPRESSION

Ischemia is a strong inducer of gene expression in the brain. Many genes are induced within minutes or hours after ligation of the middle cerebral artery ischemia, often returning to normal levels within the first 24 hours (16, 17). Less is known about late postischemic events. Considering the well-known role of the brain-derived neurotrophic factor (BDNF) in brain plasticity in intact animals (18), we have tested the hypothesis that postischemic housing in an enriched environment could lead to an enhanced BDNF gene expression. Contrary to the hypothesis, a marked increase in BDNF gene expression during days 2–12 observed in rats housed in standard environment was inhibited in rats housed in enriched environment (18). Significant differences with standard rats above and enriched rats below baseline were observed in the peri-infarct region, contralateral cortex and hippocampus 2 to 12 days after induction of ischemia. The BDNF protein levels 12 days after the middle cerebral artery occlusion likewise showed a significant reduction in the peri-infarct area but not in the contralateral hemisphere (19). A similar dampening of the postischemic gene expression in rats housed in enriched environment was seen for NGFI-A mRNA. With this gene, however, a late significant increase in the enriched group was observed 30 days after the lesion (20).

Cortical networks adjacent to a focal brain infarct are hyperexcitable because of an imbalance between excitatory and inhibitory synaptic function due to increased N-methyl-D-aspartic acid-receptor-mediated excitation and reduced GABAergic inhibition (21). Hyperexcitability has also been recorded in the contralat-

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eral hemisphere one week after middle cerebral artery occlusion (22). Both a detrimental and a beneficial plasticity-promoting role of lesion-induced hyperexcitability have been proposed (23). One possible interpretation of the BDNF data would be that early postischemic dampening of the peri-infarct neuronal hyperactivity activity might be beneficial. The possible interactions between trophic and growth inhibitory factors (24) also need to be considered. The time-related patterns of postischemic gene expressions are obviously very complex. Ten days after a phototrombotic lesion the gene expression patterns of 1176 genes, analyzed using DNA macro arrays, showed extensive changes with up-regulation on several genes in both hemispheres and down-regulation of other genes in the ipsilateral areas (25).

ENVIRONMENTAL EFFECTS ON NEURONAL MORPHOLOGY AND DENDRITIC SPINES

Dendritic spines, which are the primary postsynaptic targets of excitatory glutaminergic synapses in the mature brain, have been proposed as primary sites of synaptic plasticity (26–28) Current data indicate that the dendritic tree is covered with a variety of excitable synaptic channels operating on different time scales and with activity-dependent sensitivity enabling a sophisticated neuronal plastic capability (29).

Environmental enrichment can enhance dendritic branching and increase the number of dendritic spines and synapses in intact animals (9–11). Rearing animals in social isolation has the opposite effect (30). In intact rats, reach training has been shown to selectively alter dendritic branching in layer II and III pyramidal neurons in rat motor-somatosensory forelimb cortex (31). Housing in an enriched environment significantly increases the number of dendritic spines both in cortical layers II–III (Fig. 1) and V–VI, indicating that free activities in an enriched environment lead to a more general stimulation of dendritic spines (32, 33). Rats postoperatively housed in an enriched environment had significantly more spines in pyramidal neurons in layers II–III than rats in standard cages in the cortex contralateral to the infarct cavity. Neurons in layers II–III have extensive connection with other cortical areas, and synaptic plasticity in cortical horizontal connections is proposed to underlie cortical map reorganisation (34). In the deeper cortical layers, both enriched and standard rats had a reduced number of dendritic spines, presumably related to the extensive loss of callosal connections from the infarct area.

ENVIRONMENTAL EFFECT ON LESION-INDUCED PROGENITOR CELL DIFFERENTIATION

Environmental enrichment can enhance neurogenesis in intact animals (35–37). With the aim to study if it also influences lesion-induced neurogenesis, rats were placed in an enriched environment either 24 h or 7 days after an occlusion of the middle cerebral artery distal to the striatal branches. BrdU, a marker of cell division, was giving during the first week following the occlusion. Whereas there was no difference in net survival of newly formed cells between enriched and standard animals 4 weeks later, both enriched groups normalised the neuron to astrocyte ratio in

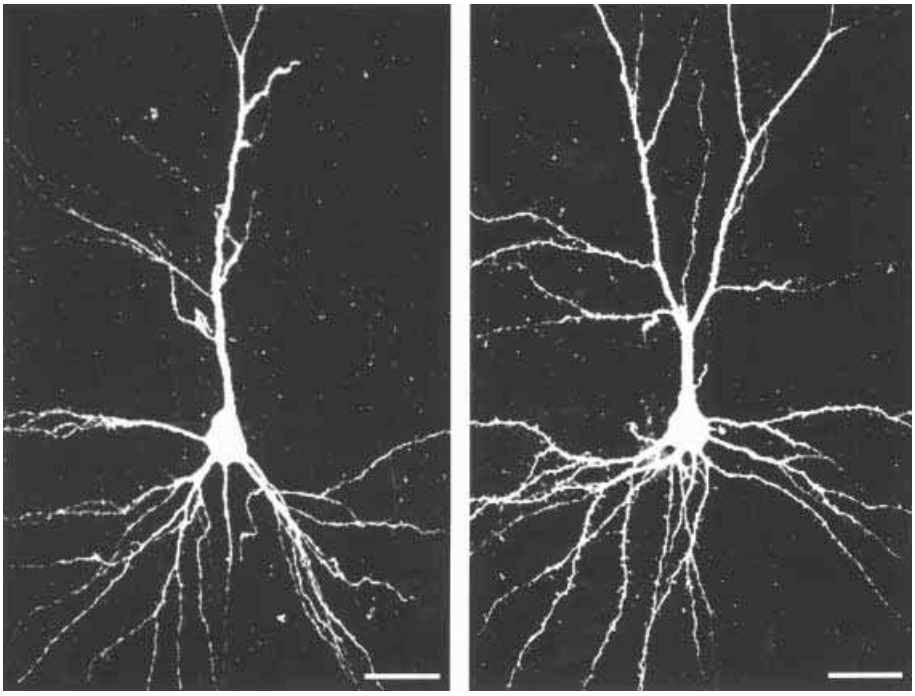

Fig. 1. Dendritic branching of pyramidal neurons in layer III in somatosensory cortex in rats housed in standard *(left)* or transferred to an enriched *(right)* conditions for 3 weeks. Confocal imaging after microinjection of Lucifer yellow. From Johansson & Belichenko (33) by permission.

the newly formed cells in the hippocampus, a ratio that was manifold increased in postischemic rats housed in standard environment because few new astrocytes were formed (38). A low number of astrocytes may be insufficient to support the newly formed neurons. So far most studies on brain plasticity have concentrated on neuronal changes. There is increasing evidence, however, that astrocytes take an active part in synaptic plasticity (39–44), and ultrastructural evidence for increased contact between astrocytes and synapses in rats reared in a complex environment suggests a close relationship between astrocyte plasticity and experience-induced synaptic plasticity (45).

ENVIRONMENT, SOCIAL INTERACTION AND PHYSICAL ACTIVITY

Enriched environment includes opportunities for various physical activities and social interaction. Studies aimed at comparing the effect of enriched environment with that of social interaction and repetitive physical exercise in the form of wheel running have shown that social interaction was superior to running and that enriched environment resulted in the best performance (13, 14). These results are in agreement with a study on intact animals that indicated that social grouping could not account for the full effects of enriched environment (46). Likewise, in a study comparing the effect of exposure to enriched environment versus running before inducing bilateral cortical lesions, running did not yield the same protective effect from postoperative impairment as enriched environment did (47). Based on studies on stem cell proliferation and survival in the rodent hippocampus it has been proposed that an increase in voluntary exercise might be responsible for most beneficial effects of environmental enrichment in intact animals (48) and physical exercise has been proposed to enhance brain health and plasticity (49). There is little doubt that physical activity is essential for keeping the vascular system in good shape and thus can help reduce stroke incidence. Furthermore, there is evidence that preclinical physical activities are important for outcome in patients after stroke (50). However, experimental studies have shown that motor learning but not repetitive physical exercise generates new synapses in the cerebellar cortex in adult rats (51, 52), and that skill learning but not strength training induces cortical reorganisation (53). Likewise, extensive repetition of digit movements in the absence of motor learning did not alter digit representations within the primary motor cortex of the squirrel monkey (54). One important factor in enriched environmental housing is the fact that the environment is changed and new objects are included a few times a week. The fact that environmental enrichment induces a widespread increase in dendritic spines (32, 33), enhances the effect of skill training (55) and interacts with other interventions as described below indicates in my view that repetitive muscle training is not the major or only effect of an enriched environment.

ENVIRONMENTAL INTERACTION WITH NEOCORTICAL TRANSPLANTATION AND DRUGS

In adult rats, foetal neocortical tissue transplanted in the infarcted area 1–9 weeks after the ischemic event survives and receives afferent connections from ipsilateral and contralateral cortex, the thalamus and several other host brain subcortical nuclei (56). Although sensory stimulation of the rat vibrissae enhances the metabolic activity in grafts, indicating that such connections can be functionally relevant (57), no effect on functional outcome is observed unless the rats are housed in enriched environment (58, 59). When grafting was performed three weeks after the arterial ligation there was no significant difference between grafted and non-grafted infarcted rats housed in an enriched environment, and both groups improved significantly more than grafted rats in standard environment. However, if grafted one week after the arterial ligation, the enriched environment further enhanced functional outcome, and the secondary thalamic atrophy was significantly reduced (59). Furthermore, afferent connections from the host brain develop more extensive connections within the graft in rats housed in enriched environment (60). These results are consistent with studies from other neural grafting models (61).

Selegiline, an irreversible monoamine oxidase B inhibitor, which alone has no beneficial effect after focal cerebral ischemia, reduces behavioural and cognitive deficits when combined with housing in enriched environment (62). In the opposite direction, amphetamine, which in other experimental studies has been shown to improve outcome, had no additional effect in rats housed in enriched environment (63), and unpublished data indicate that diazepam has no negative effect in rats housed in enriched environment either. The additive or neutralising effects of stimulating environments on drugs may perhaps be explained by the release of catecholamines, glutamate and a number of hormones induced by physical activities (64). The interaction between drugs and environment is clearly an area that needs more attention.

ARE EXPERIMENTAL DATA ON ENRICHED ENVIRONMENT RELEVANT FOR STROKE PATIENTS?

The animal data presented above demonstrate that postischemic environmental intervention can influence outcome after focal brain ischemia. As for the relevance for human stroke patients, two arguments can be raised. One is that standard laboratory housing is a deprived environment not comparable to normal human life and thus the result obtained in animal studies may not be relevant for patients. This is a valid argument, which, however, leads to the conclusion that a stimulating environment should be the base in all animal recovery studies to which specific rehabilitative interventions can be added. An opposite argument would be that some elderly stroke patients might have lived a rather isolated

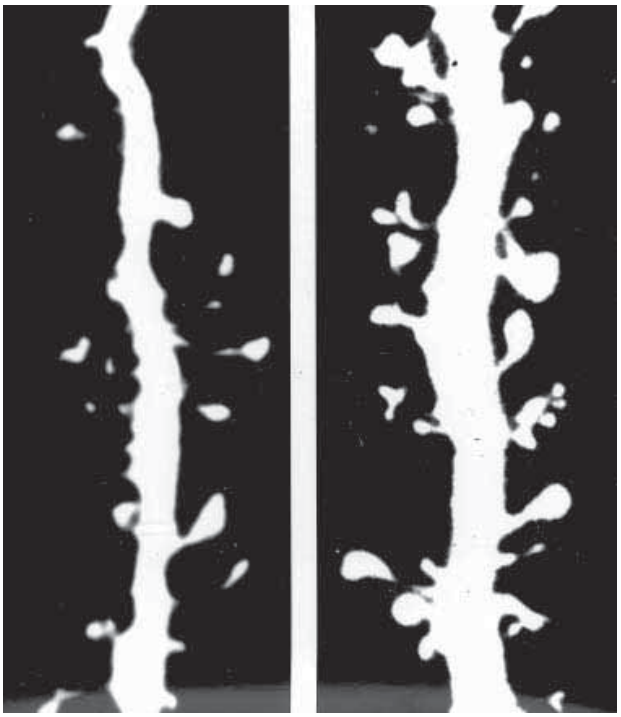

Fig. 2. Dendritic spine density and morphology in rats housed in standard environment (*left*) and enriched environment (*right*).

life before stroke onset, also a valid argument considering the fact that half of the stroke patients in e.g. Sweden are 75 years or older. In any case, for most patients, the transfer from home to hospital after an acute stroke involves a drastic change in environment that justifies attempts to optimise the hospital and rehabilitation environment.

CLINICAL DATA

There are no randomised clinical studies comparable to the animal studies described above. Because early mobilisation can reduce secondary thromboembolic events, pneumonia, and mortality in acute stroke, it is recommended in many countries that stroke patients be admitted to stroke units with specially trained medical and nursing staff, co-ordinated multidisciplinary rehabilitation, and education programs for patients and their families (66). No study has shown to what extent potential beneficial effects are due to specific rehabilitation strategies and time spent in physiotherapy and occupational therapy, or to the non-specific effect of a more stimulating environment, with competent staff that encourages and supports the patient and family. Mere admittance to a stroke unit may increase the expectations of stroke patients. Expectation plays a significant role in drug treatment and other interventions. Current neuroimaging data suggest that expectation in the form of placebo treatment can lead to biochemical and neurobiological events related to the medical problem treated. Thus there is evidence that placebo and opioid analgesia share a neuronal network (66), that placebo treatment in depressed patients induces some of the effects of antidepressant drugs possibly related to dopamine and endorphin (67), and that systemic injections of saline in patients with Parkinson's disease can induce dopamine release in the brain (68). Could stroke units be considered an enriched environment and, if so, could they have the effect of reducing post-stoke depression or improving cognitive functions after stroke? These comments are clearly speculative and no corresponding hypotheses have to my knowledge been tested.

A small retrospective study published 20 years ago indicated that the view a patient saw through his or her window influenced recovery after abdomen surgery, i.e. patients who could look out over a park left the hospital earlier and needed less drugs than those looking at a wall (69). Both ancient and contemporary literature are full of stories about how our environment and activities influence our lives in health and disease. Perhaps future research will find some evidence to support such widely held human beliefs.

CONCLUDING REMARKS

Clinical studies indicate that the patient's attitude, activities and social interaction may influence the functional outcome and quality of life after stroke (70). However, it is difficult to separate genetic and environmental factors in patients. Every patient is unique. The capability to handle crises, including sickness and disease, varies. Rehabilitation strategies that are meaningful for the individual patients are likely to be the most effective. Perhaps it is particularly important in neurorehabilitation to stimulate patients with little initiative of their own. It is important to set goals that are attainable for the individual patient. What is an enriched environment for patients will differ according to personality and earlier life experiences. The role of music and art in cognitive rehabilitation, for instance, has so far been little explored.

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