Treatment research

Pharmacologic approaches to cerebral aging and neuroplasticity: insights from the stroke model

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Brain plasticity is an intrinsic characteristic of the nervous system that allows continuous remodeling of brain functions in pathophysiological conditions. Although normal aging is associated with morphological modifications and decline of cerebral functions, brain plasticity is at least partially preserved in elderly individuals. A growing body of evidence supports the notion that cognitive enrichment and aerobic training induce a dynamic reorganization of higher cerebral functions, thereby helping to maintain operational skills in the elderly and reducing the incidence of dementia. The stroke model clearly shows that spontaneous brain plasticity exists after a lesion, even in old patients, and that it can be modulated through external factors like rehabilitation and drugs. Whether drugs can be used with the aim of modulating the effects of physical training or cognitive stimulation in healthy aged people has not been addressed until now. The risk:benefit ratio will be the key question with regard to the ethical aspect of this challenge. We review in this article the main aspects of human brain plasticity as shown in patients with stroke, the drug modulation of brain plasticity and its consequences on recovery, and finally we address the question of the influence of aging on brain plasticity.

Introduction

Plasticity of the human brain has been extensively studied during development. Children who had undergone hemispherectomy for intractable epilepsy and who showed a remarkable recovery of motor function or language probably represent the most illustrative example of brain plasticity and its correlation with recovery from a neurological deficit. On the other hand, plasticity of the adult brain tends to remain an uncommon concept; plasticity does go somewhat against the traditional phrenologic approach to the human brain. Broca gave strong support to localizationist concepts of brain function when he correlated, in 1861, a lesion of the left temporal lobe with aphasia. Little room was available for the notion of brain plasticity during that period, despite significant reports of clinical recovery from neurological deficits. However, evidence for plasticity of the adult brain has more recently (in the last 30 years) been recognized. It is now accepted that recovery after a brain lesion can continue for years. Hemispherectomy, experiments with sensory substitution, muscle transposition after motor deficit, and facial paralysis which recovered after VII-XII cranial anastomosis strongly pleaded in favor of a certain capacity for plasticity of the adult human brain. Moreover, the daily clinical practice of neurologists provides strong

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arguments for capacities of reorganization of the adult human brain after a lesion. For example, recovery of function can represent an argument for the diagnosis of stroke in patients who have undergone a focal neurological deficit of abrupt onset.[1-6]

Stroke greatly differs from neurodegenerative diseases as it is a consequence of a single acute focal lesion of the brain. A heavy burden for our society, it results in a large number of deaths and prolonged neurological deficits in many patients. Recovery from stroke represents a major issue for these patients, and is a good illustration of brain plasticity. Stroke occurs more frequently in aged people; more than 50% of strokes involve people over 85. The question of the influence of aging on brain plasticity can be indirectly addressed through the capacity of aged people to recover from a stroke. Clinicians know that complication from stroke in the elderly comes not only from the stroke itself but also from the associated comorbidities. So it is not so easy to answer the question, even if many observations both in animal models and in humans have shown that brain plasticity is reduced with aging. Although normal aging is associated with morphological modifications and decline of cerebral functions, it is however accepted that brain plasticity is probably at least partially preserved in elderly individuals.

The capacity of the brain to reorganize after a lesion in order to compensate for a neurological deficit is a major issue for clinicians and for patients, and is a convincing illustration of brain plasticity. However, brain plasticity is probably more complex and more generally participates in our capacity to interact with the external environment. It is known for example that learning induces changes in the brain circuitry, and that the acquisition of new skills elicits diffuse modification in brain neuronal networks. Moreover, it is likely that relearning, which is the basis of rehabilitation procedures in patients with neurological deficits, uses similar principles in lesioned networks of the human brain.[7-12]

Finally, although plasticity of the human brain can be investigated through learning about and following up brain lesions, other external agents can play a decisive role in the functional modification of brain neuronal networks. This is definitely the case for medications. It is clear that Parkinson's disease provides an excellent example to demonstrate that the administration of even a single dose of L-DOPA can dramatically change the organization of motor cortices, in particular the supplementary motor area. The question of external modulation of human brain plasticity by drugs or more generally by so-called restorative therapies has been extensively studied in the past few years, and significant advances have shown that monoaminergic drugs both in animal experiments and in limited clinical trials improve recovery from focal brain lesions. In particular, a recent clinical study has demonstrated that monoaminergic SSRIs were able to improve motor recovery after stroke. So we now know that drug modulation of human brain plasticity is a reality, and that it opens up new perspectives in the treatment of patients.[13-20]

We review in this article the main aspects of human brain plasticity as shown in patients with stroke, the drug modulation of brain plasticity and its consequences on recovery, and finally we address the question of the influence of aging on brain plasticity.

Brain plasticity after stroke

Cellular processes

Basic cellular phenomena

With respect to outcome, the impact of the different cellular processes that occur during the first days after stroke onset are not yet known. However, they have been described in basic research and animal experiments. Cellular dysfunction including cell death, metabolic depression, inflammation, blood-brain barrier leakage, and axonal growth inhibition, starts immediately after stroke. Early reperfusion techniques aim at limiting damage and reversing cellular dysfunction. Reperfusion damage includes the formation of free radicals, vasogenic edema, leukocyte infiltration, and activation of microglia.[14]

The cellular mechanisms involved in brain plasticity are distinct. They have been described in animal models. Some of them correspond to functional modifications of the brain circuitry (unmasking of existing synapses, release of inhibition), others correspond to anatomical phenotypal changes in the brain neuronal network (synapse sprouting).

The unresolved question of neurogenesis and angiogenesis

In the adult human brain, neural stem cells keep producing new neurons, astrocytes, and oligodendrocytes in

two defined regions: the dentate gyrus of the hippocampus and the subventricular zone, albeit at a much lower rate than during earlier ontogenetic stages. We do not yet know the functional significance of adult mammalian neurogenesis, because no animal models exist in which neurogenesis could be specifically inhibited without simultaneous inhibitory or modulatory effects on other plasticity responses. However, an enriched environment applied to adults of various vertebrate species stimulates both baseline and ischemia-triggered neurogenesis. Thus, it is possible that newly formed neurons, astrocytes, or oligodendrocytes positively affect brain plasticity and functional recovery after stroke.

Angiogenesis, the formation of new vessels, plays an important role in remodeling of ischemic brain tissue after stroke through enhanced perfusion as well as blood flow–independent mechanisms.[21-25]

Cerebral plasticity promotion

Recent laboratory findings suggest that it might be possible to promote cerebral plasticity and neurological recovery after stroke by use of exogenous pharmacological or cell-based treatments.[14] Brain microvasculature and glial cells respond in concert to ischemic stressors and treatment, creating an environment in which successful recovery can ensue. Neurons remote from and adjacent to the ischemic lesion are able to sprout, and neural precursor cells that accumulate with cerebral microvessels in the perilesional tissue further stimulate brain plasticity and neurological recovery. These factors interact in a highly dynamic way, facilitating temporally and spatially orchestrated responses of brain networks. They all contribute to making our relationship with our environment as close as possible.

Evidence for brain reorganization after stroke

It is one of the goals of modern neuroimaging to identify the post-lesional changes in the human brain. The past few years have seen a tremendous development of technology. Positron emission tomography (PET) cameras now have greatly improved spatial resolution, and have simplified data acquisition and processing. Magnetic resonance imaging (MRI) and functional MRI now combine analysis of anatomy and function. EEG, event-related potential, and and magnetoencephalography have undergone a considerable development in sig-

nal post-processing and in source localization with new realistic models. Other techniques such as magnetic stimulation have been combined with previous ones in order to improve the data and find the best compromise between spatial and temporal resolution of the techniques. These technical improvements have provided new data regarding spontaneous post-stroke brain plasticity in humans.

Observed phenomena

Reorganization of brain metabolism, recruitment of remote areas, overactivation of cortices, and changes in cortical maps have been identified as the main observed changes in patients with stroke undergoing at least partial recovery of neurological function.[26-29] Recruitment of remote areas has been shown both in patients with motor deficit and in patients with aphasia. It concerns both primary and associative cortices. This is particularly the case for premotor cortex, supplementary motor area, and inferior parietal cortex, through anatomical identified projection on the corticospinal tract. Changes in cortical maps were demonstrated in recovering stroke patients with upper-limb motor deficit, as it had been before in patients with peripheral facial palsy or in patients with amyotrophic lateral sclerosis. While motor and premotor cortices were overactivated compared with controls, the peak of fMRI activation was located 5 mm to 10 mm below the M1 hand area in the area governing the face motor control. Posterior translation towards P1 of the peak of activation was also observed. This probably corresponds to the unmasking of neuron activity. Contralesional axonal remodeling of the corticospinal system has been demonstrated only recently in animal model experiments. However, the capacity for remodeling of the corticospinal tract axons at the spinal cord level remains to be demonstrated in stroke patients.[26-29]

Time course

It is now well established that these phenomena can not be observed in all patients and at all stages of the post-stroke recovery period. Many studies using neuroimaging techniques have contributed to better understanding of the time course of the observed intracerebral reorganization phenomena with regard to clinical recovery of neurological functions. For example, in aphasic patients studied at the acute phase of the stroke and 1 year later, the

improvement of the clinical aphasia scores was associated with a strong reduction in the number of activated areas of the linguistic network. This was also observed in motor-recovering patients. Briefly, in patients with good recovery, linguistic networks were close to those observed in normals, while in patients with poor recovery a much more widespread activation of remote areas was still observed. This is a general trend, with many different individual data. Post-lesional intracerebral reorganization can vary greatly between subjects and we do not know what the determinants of such variability are.[30-34]

Brain plasticity and functional recovery

There is some logical thought in correlating brain postlesional spontaneous plasticity with clinical recovery of neurological function and in thinking that brain plasticity represents the rational biological basis of recovery. However, this assumption has been challenged on the basis that brain plasticity was similarly observed in other diseases with no clinical recovery like amytrophic lateral sclerosis or Alzheimer's disease (AD). It is now demonstrated that brain reorganization and functional recovery are closely linked in the poststroke period.[30-34] For example it has been shown in hemiplegic patients that motor scale changes were correlated with activation or deactivation of motor network areas. Other studies have underlined that some anatomical region of the motor system like the posterior part of primary motor cortex were key regions for recovery. An early activation of this was correlated with good recovery. Accurate prediction of motor recovery assists rehabilitation planning and supports realistic goal-setting by clinicians and patients. Initial impairment is negatively related to degree of recovery, but interindividual variability makes accurate prediction difficult. Neuroimaging and neurophysiological assessments can be used to measure the extent of stroke damage to the motor system and predict subsequent recovery of function, but these techniques are not yet used routinely.[11]

Pharmacological modulation of brain plasticity by monoamines

Monoaminergic drugs and motor recovery after stroke

Many monoaminergic drugs have been tested in small- or middle-sized clinical trials in patients with stroke.

Amphetamines were probably the most studied, including a total of 287 patients. Only the first two studies were able to demonstrate beneficial effects. Walker-Batson et al administered 10 mg D-amphetamine every fourth day, coupled with physiotherapy.[36] Changes of motor performance were evaluated with the Fugl–Meyer Motor Scale. Subsequent studies failed to show a superiority of D-amphetamine compared with placebo, even though some of these studies used the same protocols as one of the early intervention studies. Despite positive trials and with regard to negative ones, a recent review summarized that it is currently impossible to draw any definite conclusions about the potential role of D-amphetamine in motor rehabilitation.[19,35-41]

Methylphenidate produces an increase in dopamine signaling through multiple actions. A prospective, randomized, double-blind, placebo-controlled trial with 21 patients early after stroke indicated that the combination of methylphenidate with physiotherapy over a period of 3 weeks improved motor function (as measured with the Fugl–Meyer Motor Scale and with a modified version of the Functional Independence Measure) and decreased depression.[42] A subsequent neuroimaging study by Tardy et al confirmed these findings.[43]

Levodopa gave conflicting results, both in single-dose and in chronic dose trials. A randomized study with stroke patients (n=53) 6 weeks after stroke onset demonstrated that 100 mg levodopa given once a day over a period of 3 weeks in combination with carbidopa was significantly better than placebo in reducing motor deficits as measured with the Rivermead Motor Assessment. The improvement persisted over the subsequent 3 weeks. However, the study results have not been replicated by others up to now and a recent study with subacute stroke patients who received 100 mg levodopa per day for 2 weeks did not find a greater improvement of motor functions than in the group treated with placebo.[44-46]

Some other drugs like piracetam, reboxetine (an SNRI), donepezil (an inhibitor of acetylcholine esterase), and moclobemide (an inhibitor of monoamino oxidase A), have been tested in small series with variable results, which prevent any conclusion being drawn on their efficacy.[46-51]

Until now, there has been only limited evidence supporting or refuting the use of centrally acting drugs to enhance effects of neurorehabilitation. Many reasons have been given to explain the difficulties encountered

by the investigators: small number of patients, recruitment of patients (25 to 40 screened for 1 enrolled), heterogeneity in stroke types, size, location of lesion, concomitant neurological symptoms (within-subject variability in recovery), standardization of rehabilitation programs, dose of the drug, specific chemical formulation of the drug under study (d or dl amphetamines), time of prescription, duration of treatment, and more. However, new data obtained with SSRIs have given some hope.

SSRIs and stroke: new data

Few clinical trials with serotonin reuptake inhibitors have been reported. They have all included small numbers of patients; however, all of them suggest a positive effect on recovery after stroke. In an early trial, fluoxetine and maprotiline were tested against placebo for 3 months in patients with hemiplegic stroke patients enrolled 1 to 6 months after the stroke. The patients in the fluoxetine group (n=16) had a better outcome than those in the maprotiline or placebo groups. Acler and colleagues confirmed this finding in ten patients in the active-treatment group versus ten in the placebo group. In a double-blind, placebo-controlled crossover trial, Zittel and colleagues investigated the effects of a single dose (40 mg) of citalopram in eight patients with chronic stroke. Dexterity was significantly improved.[52-57]

The proof of concept came from studies investigating both recovery and the influence of the drug on brain activation and electrophysiology. In a double-blind placebo-controlled study by our group, Pariente and colleagues, by combining clinical motor testing and functional MRI motor assessment in patients recovering from post-stroke hemiplegia (n=8), showed that a single dose (20 mg) of fluoxetine improved hand motor function and was correlated with an overactivation of motor cortices on functional MRI. In a subsequent double-blind, placebo-controlled trial in healthy individuals, transcranial magnetic stimulation showed that the intake of a single dose of the serotonin reuptake inhibitor paroxetine was associated with hyperexcitability of the primary motor cortex, whereas chronic intake was associated with hypoexcitability of the brain motor cortices. Serotonin reuptake inhibitors increase interneuron-facilitating activity in the primary motor cortex. This study demonstrated that, in recovering stroke patients, a single dose of 20 mg transiently improved motor function and acted directly on overactivating motor cortices through a fluoxetine-induced change of cortical excitability.[58,59]

The FLAME trial was then designed with aim at investigating whether fluoxetine would enhance motor recovery if given soon after an ischemic stroke to patients who have motor deficits.[60] In a double-blind, placebo-controlled trial, patients who had ischemic stroke and hemiplegia or hemiparesis, had Fugl-Meyer motor scale (FMMS) scores of 55 or less, and were aged between 18 years and 85 years were eligible for inclusion. They were randomly assigned to fluoxetine (20 mg once per day, orally) or placebo for 3 months starting 5 to 10 days after the onset of stroke. All patients had physiotherapy. The primary outcome measure was the change on the FMMS between day 0 and day 90 after the start of the study drug. A total of 118 patients were randomly assigned to fluoxetine (n=59) or placebo (n=59), and 113 were included in the analysis. FMMS improvement at day 90 was significantly greater in the fluoxetine group (adjusted mean 34·0 points [95% CI 29·7–38·4]) than in the placebo group (24·3 points [19·9–28·7]; P=0·003).

This study shows for the first time that in patients with ischemic stroke and moderate-to-severe motor deficit, the early prescription of fluoxetine with physiotherapy enhanced motor recovery after 3 months. Long-term effects remain unknown but other studies suggest that the benefit persists after 1 year.[61]

Modulation of spontaneous brain plasticity by drugs is a promising pathway for treatment of patients with ischaemic stroke and moderate to severe motor deficit. It is now demonstrated through the model of stroke that brain plasticity can be pharmacologically modulated. The field is now wide open. The question of the influence of aging remains.

The influence of aging on brain plasticity

The question of the influence of aging both on spontaneous brain plasticity and on modulated brain plasticity is of major importance. It is not easy to address, as there is no objective individual measurements of brain plasticity. So conclusions are indirect and subject to the quality of clinical trials measuring the effect of intervention on clinical changes. Intuitively, it can be supposed that aging reduces the capacity of the lesioned brain to reorganize in neurological disorders. It is well known in the stroke field for example that the magnitude of recovery

after focal lesion is greater in children than in older adults. However, we can find in the literature arguments both for and against the capacity of the older brain to adapt to pathological conditions. We can also find arguments to positive or negative effects of drug plasticity changes in aged people.

From basic science

Brain plasticity in old animals

Arguments can be found in the literature for compromised brain remodeling and plasticity associated with age.[62-67] Arguments are summarized in a remarkable review by Hermann and Chopp.[21] Aged rats respond to plasticity-promoting therapies, but age might have an effect on some of the processes targeted by neurorestorative interventions. Improved neurological recovery associated with preservation of pyramidal tract axons ipsilateral to the stroke and enhanced pyramidal tract sprouting contralateral to the stroke was identified in 25-month-old or 12-month-old rats with ischemia treated with neutralizing anti-NogoA antibodies, pharmacological compounds, or bone-marrow-derived stromal cells. Although neurological recovery was successful, dendritic and synaptic plasticity of hippocampal CA3 and CA1 pyramidal and dentate gyrus granule cells was not influenced by anti-NogoA antibodies in old rats.

The expression of plasticity-related proteins in neurons differs between young and old animals. An effect of age was not only seen for neuronal sprouting, but also for neurogenesis and angiogenesis. The numbers of proliferating neural precursor cells in the subventricular zone and subgranular layer were lower in the brain tissue of 15-month-old rats than in that of 3-month-old rats, both under normal physiological and ischemic conditions. Although the de novo generation of neurons in the ischemic striatum was very similar in both groups, neurogenesis was decreased in the dentate gyrus of 15-month-old rats when exposed to focal cerebral ischemia. Reduced neurogenesis in old animals could be related to lower expression of VEGFR2 on the surface of neural precursor cells. Although evidence is limited to a rather small number of studies, the preserved neurological recovery in old animals argues against specific age limits for neurorestorative treatments. Despite this evidence, the effects of age need to be controlled in clinical proof-of-concept studies.[62-67]

Comorbidities, vascular risk factors, and brain plasticity

Vascular risk factors are often associated with stroke and so also with aging.[68-71] They are part of the question and we can find also arguments in basic science for compromised brain remodeling and plasticity associated with vascular risk factors. Experimental studies poorly mimic comorbidities, because experiments are done mainly in animals that are otherwise healthy. The relevance of associated diseases for the efficacy of plasticity-promoting therapies was recently shown in rats with streptozotocin-induced diabetes. Paradoxically, treatment with bone-marrow-derived stromal cells did not improve neurological recovery in rats with diabetes, but increased mortality, blood–brain barrier leakage, and brain hemorrhage. In histochemical studies, neo intima formation and arteriole narrowing were exacerbated by bone-marrow-derived stromal cells in rats with diabetes, as was macrophage accumulation in blood vessels. These abnormalities were attributed to increased angiogenin expression in the brain and brain-supplying arteries of rats with diabetes. Investigators suggest that treatment with bone-marrow-derived stromal cells should not be considered in patients with diabetes. Three-quarters of stroke patients have arterial hypertension, and about half of patients have hypercholesterolemia. In spontaneously hypertensive rats, subtle abnormalities in the expression of neurotrophic factors and their receptors have been described in the dentate gyrus. Whether these findings are true for prolonged arterial hypertension, which causes cerebral microangiopathy in human beings, remains to be shown. Hypercholesterolemia reduces angiogenesis and promotes blood–brain barrier permeability. These vascular changes are driven by many factors. In rats with cerebral ischemia, vitamin B3 administration, which elevates high-density lipoprotein and thereby reduces serum cholesterol, increased angiogenesis, and improved neurological recovery. Moreover, despite limited evidence, recent studies suggest that impaired angiogenesis in patients with hypercholesterolemia parallels disturbances in synaptic plasticity. Lipid-lowering drugs, especially statins, are widely prescribed for stroke patients as secondary stroke prevention. Statins also have neurorestorative properties.

From clinical data

Clinical data mainly do not confirm basic science evidence of the reduced capacity of brain to reorganize

after a focal lesion or during a chronic neurodegenerative disease in aging. Even if we have clinical arguments to say that post-stroke clinical recovery is reduced in old people, clinicians have all seen remarkable recovery in patients over 85. Moreover, it has been recently demonstrated that IV thrombolysis could be beneficial in people over 80 as recently shown in IST3 trial.[72] Thus, even if the biological counterpart of brain plasticity is reduced in old age, clinical recovery exists in old people. The stroke model has shown this. This preserved capacity is much more difficult to demonstrate in chronic degenerative disease where recovery does not exist.

However, we know that people with memory disturbances in early AD are able to recruit alternative brain networks to perform a memory task. This has been shown with fMRI by Pariente et al.[73]

Interventional studies also provide evidence for preserved brain capacity to reorganize in the elderly.[74-84] Substantial evidence indicates that physical activity enhances learning and memory for people of all ages, including individuals who suffer from cognitive impairment. The mechanisms that underlie these benefits have been explored using animal models, including transgenic models of AD and the influence of interventions has been showed. Accumulating research shows that physical activity reinstates hippocampal function by enhancing the expression of brain-derived neurotrophic factor (BDNF) and other growth factors that promote neurogenesis, angiogenesis, and synaptic plasticity. In addition, several studies have found that physical activity counteracts age- and AD-associated declines in mitochondrial and immune system function. A growing body of evidence also suggests that exercise interventions hold the potential to reduce the pathological features associated with AD.

Taken together, animal and human studies indicate that exercise provides a powerful stimulus that can counter the molecular changes that underlie the progressive loss of hippocampal function in advanced age.[75,76] So even if spontaneous neurological disease brain reorganization is reduced in the elderly, both clinical and basic science data demonstrate that intervention has a clinical and a biological positive effect. Some other examples can be found with cognitive enrichment protocols. Aging is a major co-risk factor in many neurodegenerative diseases. Cognitive enrichment positively affects the structural plasticity of the aging brain. The effects of a set of 6-month structured multimodal activities (Combination

Training; CT) on cognitive performances, functional connectivity, and cortical thickness were evaluated in a group of healthy elderly individuals.[77] In this study combination training improves cognitive/occupational performances and reorganizes functional connectivity. Intriguingly, individuals responding to CT showed specific dopamine-related genotypes. The findings support the idea that exposure to a set of structured multimodal activities can be an effective strategy to counteract aging-related cognitive decline and also indicate that significant capability of functional and structural changes are maintained in the elderly.

Exercise training consequences on brain structure have also been investigated using neuroimaging tools. Liu-Ambrose et al[74] have shown that 12 months of twice-weekly resistance training led to functional changes in two regions of cortex previously associated with response inhibition processes—the anterior portion of the left middle temporal gyrus and the left anterior insula extending into lateral orbital frontal cortex—in community-dwelling senior women. These hemodynamic effects co-occurred with improved task performance.

Although normal aging is associated with morphological modifications and decline of cerebral functions, brain plasticity is at least partially preserved in elderly individuals and can be modulated by external intervention like exercise or cognitive stimulation. Whether drugs can be used with aim at modulating the effects of physical training or cognitive stimulation in healthy aged people has not been addressed until now. The risk:benefit ratio will be the key question with regard to the ethic aspect of the challenge.

Genetic polymorphism

Genetic polymorphism is one factor that may influence the response of the brain to injury and disease. BDNF has a critical role in activity-dependent modulation of synaptic plasticity in human motor cortex.[85-89] A common single nucleotide polymorphism (BDNFval66met), which results in reduced secretion of BDNF, reduces the activity-related cortical plasticity in response to motor training in healthy individuals and is associated with greater error and poorer retention in short-term motor learning. In a cohort of 722 elderly individuals, the presence of the polymorphism was associated with significantly reduced cognitive performance on processing speed, delayed recall, and general intelligence. It has also

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been proposed to be a predictor of poor outcome among survivors of aneurysmal subarachnoid hemorrhage. There are likely to be other genetic differences that can influence outcome. This remains an open field.

Conclusion

Brain plasticity is an intrinsic characteristic of the nervous system that allows continuous remodeling of brain functions upon pathophysiological conditions. Although normal aging is associated with morphological modifications and decline of cerebral functions, brain plasticity is preserved in elderly individuals. A growing body of evidence supports the notion that cognitive enrichment and aerobic training induce a dynamic reorganization of higher cerebral functions, thereby helping maintain operational skills in the elderly and reducing the incidence of Alzheimer's disease. The stroke model clearly shows that spontaneous brain plasticity exists after a lesion even in old patients, and that it can be modulated through external factors like rehabilitation and drugs. Whether drugs can be used with the aim of modulating the effects of physical training or cognitive stimulation in healthy aged people has not been addressed until now. The risk:benefit ratio will be the key question with regard to the ethical aspects of the challenge. ❏

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Enfoques farmacológicos del envejecimiento cerebral y la neuroplasticidad: reflexiones a partir del modelo de accidente cerebro vascular

La plasticidad cerebral es una característica intrínseca del sistema nervioso que permite una continua remodelación de las funciones cerebrales en situaciones fisiopatológicas. Aunque el envejecimiento normal está asociado con cambios morfológicos y una declinación de las funciones cerebrales, en sujetos de edad avanzada la plasticidad del cerebro se mantiene parcialmente. Cada vez hay mayor evidencia que sustenta la noción que el enriquecimiento cognitivo y el entrenamiento aeróbico inducen una reorganización dinámica de las funciones cerebrales superiores, con lo que ayudan a mantener las habilidades operacionales en el anciano y reducen la incidencia de demencia. Claramente el modelo de accidente cerebro vascular muestra que la plasticidad cerebral espontánea se produce después de la lesión, inclusive en pacientes de edad avanzada y que puede ser modulada a través de factores externos como la rehabilitación y los fármacos. Hasta la fecha no se han identificado fármacos que puedan ser empleados con el objetivo de modular los efectos del entrenamiento físico o de la estimulación cognitiva en ancianos sanos. La relación riesgo:beneficio será la pregunta clave respecto a los aspectos éticos de este desafío. En este artículo se revisan los aspectos principales de la plasticidad cerebral humana como se observa en pacientes con accidentes cerebro vasculares, la modulación por fármacos de la plasticidad neuronal y sus consecuencias en la recuperación, y finalmente se aborda la pregunta acerca de la influencia del envejecimiento en la plasticidad cerebral.

Approches pharmacologiques du vieillissement cérébral et de la neuroplasticité : un aperçu basé sur le modèle de l'accident vasculaire cérébral

La plasticité cérébrale est une caractéristique propre du système nerveux central qui permet un remodelage permanent de son activité à la fois dans des conditions physiologiques et au cours des maladies neurologiques. Bien que le vieillissement s'accompagne de modifications de structure et d'une diminution des performances cognitives, les capacités de plasticité restent au moins partiellement conservées chez le sujet âgé. Un faisceau d'arguments préclinique et clinique plaide pour un rôle majeur des stimulations cognitives et physiques dans le maintien des fonctions cognitives au cours du vieillissement. Le « modèle » de l'accident vasculaire cérébral démontre clairement que le cerveau âgé est capable de se réorganiser après une lésion unique aiguë et focale et que cette réorganisation peut être modulée par des facteurs externes tels que la rééducation et certains médicaments. On ne sait pas encore si les médicaments sont capables de moduler les effets des stimulations physique et cognitive. Les aspects éthiques et le rapport bénéfice-risque seront au cœur du débat. Nous traitons dans cet article les différents aspects de la plasticité cérébrale que l'accident vasculaire cérébral a permis de décrire, nous envisageons l'action des médicaments sur la plasticité cérébrale post-lésionnelle et la récupération fonctionnelle et nous évoquons l'influence du vieillissement sur les capacités du cerveau humain à se reconfigurer lorsqu'il est lésé.

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