Chronic depression as a model disease for cerebral aging

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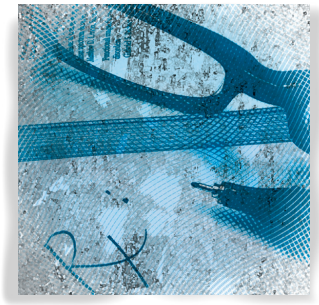

Conceptualizations of the underlying neurobiology of major depression have changed their focus from dysfunctions of neurotransmission to dysfunctions of neurogenesis and neuroprotection. The "neurogenesis hypothesis of depression" posits that changes in the rate of neurogenesis are the underlying mechanism in the pathology and treatment of major depression. Stress, neuroinflammation, dysfunctional insulin regulation, oxidative stress, and alterations in neurotrophic factors possibly contribute to the development of depression. The influence of antidepressant therapies, namely pharmacotherapy and neuroprotectants, on cellular plasticity are summarized. A dysfunction of complex neuronal networks as a consequence of neural degeneration in neuropsychiatric diseases has led to the application of deep brain stimulation. We discuss the way depression seen in the light of the neurogenesis hypothesis can be used as a model disease for cerebral aging. A common pathological mechanism in depression and cerebral aging—a dysfunction of neuroprotection and neurogenesis—is discussed. This has implications for new treatment methods.

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Traditional conceptualization of neurobiology of depression

Development of traditional pharmacological treatments for major depression has been based on *the monoamine hypothesis of depression*, inferring a depletion in the levels of serotonin, norepinephrine, and dopamine in the central nervous system as the underlying pathophysiology of depression This hypothesis is supported by the mechanism of action of antidepressants, although the mechanism of action is not precisely understood and only about 50% of patients respond to antidepressants with this action.[1] Thus, new types of antidepressants (eg, κ-receptor antagonists, melatonin receptor agonists, cytokines) are the subject of active research.[1] The antidepressant effect of neuromodulation approaches (eg, vagus nerve stimulation therapy, deep brain stimulation) have also challenged the monoamine hypothesis and favored the *network hypothesis of depression*. This hypothesis assumes that dysfunctions of large neuronal networks in the brain can be normalized through a modulation of one node of the respective network.

Keywords: *depression; cerebral aging; plasticity; neuroprotectant; neurodegeneration; Alzheimer's disease; Parkinson's disease; neuroinflammation; antidepressant therapy; deep brain stimulation; neuroplasticity*

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In this article, we will rely on another explanatory approach to depression, namely on the *neurogenesis hypothesis of depression*.[2] This hypothesis posits that changes in the rate of neurogenesis are the underlying mechanism in the pathology and treatment of major depression.[3] We then discuss in what way depression according to the neurogenesis hypothesis can be used as model disease for cerebral aging, and possible implications for new treatment methods.

Current knowledge on neurobiological effects of depression

In current concepts, depression is seen as a chronic disease with recurrent episodes in the majority of cases. About 30% of patients do not profit from conventional antidepressant treatments (psychotherapy, pharmacological, electroconvulsive therapy),[4] which leads to a chronic manifestation of the disease.
The *neurogenesis hypothesis* of depression assumes that neurogenesis is influenced negatively by stressful experiences and positively by antidepressant treatment. Alterations in neurogenesis are believed to play a decisive role in the pathology and treatment of major depression[3,5]; this view is supported by several converging lines of research.

Neurodegeneration and neurogenesis

Imaging and postmortem studies have demonstrated cellular loss in several brain areas, eg, in the prefrontal cortex and amygdala[6-9] and in the paraventricular nucleus of the hypothalamus[10] in depressed patients.[10] High lacunar volume in white matter has been observed in late-life mood disorders,[11] as has reduced hippocampal volume.[12,13] A negative correlation of the hippocampal volume and the length of the untreated depression, as well as a normalization of the hippocampal volume in remission, have been demonstrated.[13]

Neurogenesis and cellular plasticity

Adult neurogenesis was demonstrated in 1965 in rats and some years later in the human dentate gyrus of the hippocampus[14] and in the subventricular zone of the lateral ventricle.
It has been demonstrated that neurogenesis can be inhibited by physical and social stress, depression, and antidepressant treatment. Modulating factors seem to be novelty, fear, and learning.[3]
Possible mechanisms of action relating depression to a dysfunction in neurogenesis are psychological stress, glucose and insulin regulation, oxidative stress, a reduction in brain-derived neurotrophic factor (BDNF), and telomere shortening.

Psychological stress and neuroinflammation

Psychological stress and neuroinflammation lead to an activation of the limbic-hypothalamic-pituitary-adrenal (LHPA) axis and proinflammatory cytokines are released. It has been proven that inflammatory cytokines can induce neurodegeneration in depression.[15-18] For example, in 2009, Maes and colleagues concluded that chronic stress may exacerbate the release of proinflammatory cytokines and precipitate depressive episodes.[15] The administration of high levels of proinflammatory cytokines can cause changes in behavior similar to depression, and the attenuation of an inflammatory response can reduce depressive symptoms.[19,20]

Glucose and insulin regulation

Depression is often associated with higher levels of the stress-related hormone cortisol. In depressive patients suffering from hypercortisolemia, glucose and insulin regulation are abnormal. High levels of cortisol have an anti-insulin effect. In a comprehensive review, Rasgon and colleagues[21] have described how prolonged exposure to glucose intolerance and insulin resistance is associated with accelerated biological aging. Neurotoxic effects of hypercortisolemia have also been described.[22]

Oxidative stress

Oxidative stress and inflammation are also called the "evil twins" of brain aging. It has been shown that oxidative stress increases with aging while antioxidant activities decrease with higher age.[23] Oxidative stress is seen in depression and Alzheimer´s disease (AD).[24]

Brain-derived neurotrophic factor

Brain derived neurotrophic factor (BDNF) seems to play an important role in the neurogenesis hypothesis of depression. BDNF also has anti-inflammatory and

antioxidant effects. Diminished hippocampal BDNF activity impairs stem cells in the dentate gyrus, an effect related to depression.[25] Unmedicated depressive patients have decreased hippocampal serum concentrations of BDNF.[26]

Telomeres

Telomeres are DNA protein complexes that protect DNA from damage. The length of the telomeres is one marker of biological age and genotoxic and cytotoxic processes The effect of depression on telomeres has also been under research. Patients suffering from depression show premature telomere shortening,[27] probably due to inflammatory processes. In this relationship, the enzyme telomerase is thought to have anti-aging or cell-promoting effects. Telomerase has been shown to be increased in unmedicated depressed patients,[22] possibly a compensatory response to telomere shortening. High levels of cortisol lead to a downregulation of telomerase.[28]

An open question remains as to whether dysfunction in neuronal plasticity is the cause, the consequence, or a correlate of depression.

In the following section, we will summarize evidence for a positive effect of different antidepressant therapies on neuroplasticity.

The effect of antidepressant therapies on neuroplasticity and neuroprotection

Antidepressants

The effect of antidepressants on neuroplasticity has been under research.[29] The shrinkage of neurons in the hippocampus can be reversed with antidepressants in animal models.[30,31] Treatment with antidepressants promotes neurogenesis, thus normalizing hippocampal volume.[12,13] The appearance of new cells in the hippocampus after treatment with antidepressants[32] has been discussed as the mechanism by which antidepressants overcome stress-induced atrophy. In animal models, hippocampal neurogenesis plays a role in the action of antidepressants,[33] but its clinical relevance for the pathogenesis of depression in humans remains to be established. A putative mechanism could be that antidepressants decrease oxidative stress,[24] reduce proinflammatory cytokines[20,34] or lead to a BDNF-dependent increase in cell proliferation.

Although the effect on neuroprotection and neurogenesis of antidepressants in animal models has been proven, studies are needed to assess this effect in humans. Currently, neurogenesis is considered as one major aspect, but other factors possibly add to the pathophysiology of depression and to pharmacological treatment effects.[3]

Neuroprotectants

Neuroprotectants are drugs acting to protect against or help repair the damaging effects of a disease an insult to the brain.

Excessive *nicotine* consumption[35,36] as well as withdrawal[37,38] has been proven to induce depression. In depressed patients, nicotine has an effect on anhedonia and mood.[39,40] The neuroprotective effect of nicotine has been demonstrated, possibly by activation of nicotinergic receptors.[41,42] Nicotine has a neuroprotective effect for example in Parkinson´s disease (PD).[43-45] Consequently, it has been proposed to use nicotinic agonists for the treatment of neurodegenerative diseases and depression.[46-48]

Alcohol and depression are highly comorbid, and high doses of alcohol induce depressive-like behaviors in normal rats,[49,50] but antidepressant effects of low doses of alcohol in a rat model of depression has been demonstrated. Light to moderate drinkers have a reduced risk of dementia and cognitive decline compared with non-drinkers,[51] and low doses of alcohol are thought to provide neuroprotection through a dampening of inflammatory processes.[51-53] The exact mechanism of neuroprotection is not known.

Other substances have antidepressant as well as neuroprotective properties, eg, the antioxidant *resveratrol* (for example, in red grapes) has proven antidepressant effects in a preclinical study[54] and also reduces the risk of AD and PD,[55-57] possibly through a mediation of neuroinflammation.[58] Curcumin, another antioxidant has proven anti-inflammatory[59,60] and antidepressant[61,62] properties, and has been proposed in the treatment of neurodegenerative disease.[63]

Ketamine, a non-competitive N-methyl-D-aspartic acid (NMDA) receptor antagonist, has anxiolytic and antidepressant effects in preclinical and clinical studies,[64-66] but its application in depression and neurodegenerative disorder remains to be determined.

Taken together, the first evidence exists that neuroprotection could also have an antidepressant and anti-aging

effect, but large clinical studies are needed to further evaluate their potential in clinical practice.

Deep brain stimulation

Deep brain stimulation (DBS) is a surgical treatment. It involves the implantation of a brain pacemaker, which constantly stimulates specific structures in the brain with electrical impulses. DBS is currently under research for the treatment of chronic, therapy-resistant depression, and other psychiatry disorders. The exact mechanism of action is not fully understood, but possibly, DBS modulates neuronal networks for emotional processing and reward, which are dysfunctional in depression. Four targets are evaluated.

DBS to the subgenual cingulate cortex (Cg25) was hypothesized to exert an antidepressant effect by modulating the depression network through a reduction of Cg25 hyperactivity.[67] Observations from historical lesion studies (eg, anterior capsulotomy) and antidepressant effects seen in patients with obsessive-compulsive disorder who were stimulated in the anterior limb of the internal capsule/the ventral striatum,[68] led to a study in which the anterior limb of the internal capsule/ventral striatum (ALIC).[69] Converging evidence from animal, pharmacological, and neuroimaging studies points toward a nucleus accumbens (NAcc) dysfunction in patients suffering from depression; this led to the hypothesis that DBS to the NAcc would lead to antidepressant effects by modulating the depression network.[70]

For all three targets (Cg25, ALIC, NAcc), similar long-term antidepressant effects have been published.[69,71-76] Response (defined as a reduction of minimum 50% in the Hamilton Rating Scale of Depression or the Montgomery-Asperg Depression Rating Scale) varied between 40% and 60%,[69,71-76] but small study sizes do not yet allow the selection of a favorite target.

Very recently, the supero-lateral branch of the medial forebrain bundle (slMFB) has also been proposed as a target.[77,78] The slMFB is anatomically and functionally connected with the above described DBS targets in depression (Cg25, ALIC and NAcc) and electric field stimulation as well as probabilistic fiber tracking have demonstrated a possible involvement of the slMFB in DBS of the current targets.[77-79] In a recent slMFB-DBS pilot study, six out of seven patients showed a fast and sustained antidepressant response.[80]

The clinical effect of DBS has been explained as a modulation of neuronal excitability and as a direct activation of neurons.[81,82] Effects of DBS on neurogenesis and neuroprotection as studied in animal models will be addressed here in more detail.

High-frequency DBS to the anterior thalamic nuclei leads has increased neural progenitors in the dentate gyrus of the hippocampus and increased number of new neurons in mice.[83] Also in rats, high-frequency (130 Hz) DBS to the same nucleus has increased hippocampal neurogenesis and restored prior experimentally suppressed neurogenesis. Low-frequency (10 Hz) DBS did not have the same effect.[84] Increased neurogenesis has been associated with enhanced behavioral performance in other studies. For example, DBS to the fornix in mice promoted proliferation in the dentate gyrus and ameliorated water maze memory after 6 weeks. This effect was missing when neurogenesis was experimentally blocked. This suggests a causal relationship between stimulation-induced promotion of adult neurogenesis and enhanced spatial memory.[85]

These animal data suggest that hippocampal neurogenesis seems a strong correlate of cognitive and emotional processes.[83] Hippocampal neurogenesis may possibly be as sensitive indicator of limbic circuitry activation induced by DBS, antidepressants (fluoxetine) and physical exercise.[83]

In a PD rat model, chronic high-frequency stimulation of the subthalamic nucleus increased cell survival in the striatum and promoted the recovery of the dopaminergic system.[86] In another study, continuous high-frequency DBS to the subthalamic nucleus for several days demonstrated delayed behavioral and cellular effects, suggesting progressive functional reorganization in the cortico-basal ganglia-cortical loop circuits.[87] Preclinical studies in both rats and monkeys have demonstrated that DBS to the subthalamic nucleus can prevent the degeneration of nigral dopaminergic neurons from the insult produced by dopamine-depleting neurotoxins.[88-91]

Although human studies are missing, subthalamic nucleus DBS in animals has demonstrated significant neuroprotective and neuroplastic properties. Thus, the initiation of DBS earlier in the course of PD has been suggested.[92] This is assumed to provide added neuroprotective benefits in addition to symptomatic relief. Currently, several studies are under way exploring the neuroprotective potential of early DBS in PD (ClinicalTrials.gov identifier: NCT00282152, NCT01274832, NCT00354133). Results

from these studies will be important for the discussion of an early intervention in other diseases, for example in depression.

Overall, deep brain stimulation has contributed to a novel view of depression—away from a synaptocentric view to a conceptualization of dysfunctional brain networks for the processing of emotions.[93] It has become evident that several neuropsychiatric disorders might be associated with network dysfunctions.[94] Initial studies have demonstrated a positive effect of DBS on neuroplasticity and neuroprotection. Future studies are required to explore long-term effects of DBS on neuroneogenesis and neuroprotection.

Aging and dementia

AD is the most common neurodegenerative disease featuring progressive impairments in memory, cognition, and behaviour, and half of the cases of dementia are caused by AD. The neurodegenerative hallmarks of AD include the accumulation amyloid-β, the deposition of amyloid plaques and the formation of neurofibrillary tangles.[95]

Similar to the monoamine theory on depression, the *cholinergic hypothesis of dementia* was proposed in 1982 by Bartus et al who believed that functional disturbances in cholinergic activity occurred in the brains of healthy older adults and demented patients.[96,97]

This hypothesis has been supported by positive effects of cholinesterase inhibitors on cognition in patients suffering from AD.[98] Although much clinical development research on cholinergic agents has followed, the clinical effects are limited[99] and no therapeutic strategy for AD has demonstrated long-term efficacy to date.[100] Thus, new concepts and therapeutic approaches are required.

The role of inflammation (eg, cytokines) and telomerase activity, which leads to neuronal degeneration[94,98] have also been suggested in the neurogenesis theory of depression. These factors lead to a dysregulation of brain networks.[99] It is unclear whether amyloid-β itself by its ability to alter synaptic (glutamatergic) transmission and to impair the induction of long-term potentiation.[99] A disruption of the connectivity of memory networks have been observable in early AD and asymptomatic individuals with high amyloid burden.[100]

Novel concepts of aging and dementia as a dysfunction of neuronal networks led to the application of deep brain stimulation in patients suffering from AD.[103] Current studies targeting the fornix or the nucleus basalis of Meynert will show whether deep brain stimulation will be superior to pharmacological treatment (ClinicalTrials.gov identifier NCT01559220, NCT01094145, NCT01608061) and if the modulation of neuronal networks as suggested effective in the treatment of depression can be extended to dementia.

Evidence for a common mechanism in depression and aging

Several lines of evidence suggest that depression and neurodegenerative diseases such as AD underlie common neurodegenerative processes, and thus depression, can be seen as a model disease for (pathological) neuronal aging.

Clinical evidence

About 50% of patients suffering from AD have comorbid depression.[104] This is especially the case in elderly patients. Many medical comorbid diseases seen in depression are diseases of advanced age (eg, heart disease, stroke).[22] In addition, both depression and AD are associated with cognitive decline.

Pathophysiology

An increase in neurodegeneration, coupled with a reduction of neuroprotection and neuronal repair, is proposed as the unifying mechanism of depression and cerebral aging.[105,106] Dysregulation of BDNF[107] and neuroinflammatory processes (eg, a dysregulation of cytokines) has been proposed as a unifying factor in depression and AD.[15] Certain cytokines increase as a function of age; this could be one cause for age-related dementia and depression.[108] A positive feedback loop between neuroinflammation, neurodegeneration, and depression has been suggested[109] and an increase in glucocorticoid level may be the initial pathological marker of depression and dementia.[105,106]

Treatment

Neuroprotectants (eg, ketamine, curcumin, resveratrol, and nicotine) seem to have antidepressant properties as well as an effect on neurodegenerative diseases (AD, PD). Electroconvulsive therapy is known to have

better results in elderly patients, although the reasons are not yet understood. Therapies (eg, pharmacotherapy, deep brain stimulation) interfering with detrimental consequences of neuronal degeneration are promising treatments both for mood disorders and cerebral aging.

Conclusion and outlook

Current concepts of depression and cerebral aging have been changed from a dysfunction of neurotransmission to a dysfunction of neurogenesis and neuroprotection. As underlying mechanisms of pharmacological treatment effects in depression and dementia, a restoration of neuroprotection and neurogenesis have been suggested. Converging evidence exists for the dysfunction of complex neuronal networks as consequence of neural degeneration in neuropsychiatric diseases, leading to the application of deep brain stimulation. Future studies using deep brain stimulation in combination with neuroimaging, electrophysiology, and cognitive behavioral experiments are required to underline the hypothesis of dysfunctional neuronal networks. ❑

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La depresión crónica como modelo de enfermedad del envejecimiento cerebral

Los conceptos neurobiológicos que están a la base de la depresión mayor han cambiado su enfoque desde las disfunciones en la neurotransmisión a disfunciones en la neurogénesis y en la neuroprotección. La "hipótesis de la neurogénesis de la depresión" postula que los cambios en la tasa de neurogénesis constituyen el mecanismo que subyace a la patología y al tratamiento de la depresión mayor. Es posible que el estrés, la neuroinflamación, la disfunción de la regulación de insulina, el estrés oxidativo y las alteraciones en los factores neurotróficos contribuyan al desarrollo de la depresión. Se resume la influencia de las terapias antidepresivas en la plasticidad neuronal, como son la farmacoterapia y los neuroprotectores. La estimulación cerebral profunda se ha aplicado a partir de disfunciones de redes neuronales complejas, producto de la degeneración neuronal en enfermedades neuropsiquiátricas. Se discute la manera en que la depresión desde la perspectiva de la hipótesis de la neurogénesis pueda ser empleada como modelo de enfermedad del envejecimiento cerebral. Se discute un mecanismo patológico común en la depresión y el envejecimiento cerebral –una disfunción de la neuroprotección y de la neurogénesis- lo que tiene efectos para nuevos métodos terapéuticos.

La dépression chronique, un modèle pathologique du vieillissement cérébral

Les concepts neurobiologiques sous-tendant la dépression majeure sont passés des dysfonctions de la neurotransmission aux dysfonctions de la neurogenèse et de la neuroprotection. « L'hypothèse neurogénésique de la dépression » postule que le mécanisme qui sous-tend la pathologie et le traitement d'une dépression majeure est celui de modifications du taux de neurogenèse. Le stress, la neuro-inflammation, un dysfonctionnement de la régulation en insuline, le stress oxydatif et des modifications des facteurs neurotrophiques peuvent participer au développement de la dépression. L'article résume l'influence des traitements antidépresseurs, c'est-à-dire des traitements pharmacologiques et des neuroprotecteurs sur la plasticité cellulaire. La stimulation cérébrale profonde est née de l'observation d'une dysfonction des réseaux neuronaux complexes suite à une neurodégénérescence lors des maladies neuropsychiatriques. Nous analysons la possibilité d'utiliser la dépression envisagée sous la lumière de l'hypothèse neurogénésique comme modèle pathologique du vieillissement cérébral. Nous étudions un mécanisme commun à la dépression et au vieillissement cérébral, une dysfonction de la neuroprotection et de la neurogenèse, ce qui a des conséquences en termes de nouvelles méthodes thérapeutiques.

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