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Pathophysiology of depression: the concept of synaptic plasticity

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Summary – Neuronal plasticity or remodeling is most often discussed with regard to cellular and behavioral models of learning and memory. However, neuronal plasticity is a fundamental process by which the brain acquires information and makes the appropriate adaptive responses in future-related settings. Dysfunction of these fundamental processes could thereby contribute to the pathophysiology of mood disorders, and recovery could occur by induction of the appropriate plasticity or remodeling. These possibilities are supported by preclinical and clinical studies demonstrating that there are structural alterations that occur in response to stress and in patients with mood disorders. Moreover, antidepressant treatment may oppose these effects by regulation of signal transduction and gene expression pathways linked to neuronal plasticity. These findings comprise a novel conceptual framework for future studies of the etiology of mood disorders and for the development of novel therapeutic interventions. © 2002 Éditions scientifiques et médicales Elsevier SAS

Antidepressant / Gene expression / Hippocampus / Neurogenesis / Neurotrophic factor / Stress

INTRODUCTION

Significant advances have been made in characterizing the adaptive changes or plasticity that contribute to learning and memory. However, neuronal plasticity or remodeling is a fundamental concept that underlies central nervous system function as it relates to many types of experience. Simply put, neuronal plasticity is the ability to acquire information and make the appropriate responses to the same or related future stimuli. This includes sensory, cognitive, emotional, social, as well as endocrine inputs and combinations of this information. Therefore, it is likely that plasticity or remodeling also plays a significant role in the pathophysiology and treatment of major psychiatric illnesses, such as mood disorders. Recent preclinical and clinical studies support this possibility, demonstrating alterations at the molecular and structural levels in response to stress and in depressed patients. The focus of this paper is to provide a brief overview of this work.

STRUCTURAL ALTERATIONS IN THE PATHOPHYSIOLOGY AND TREATMENT OF MOOD DISORDERS

It is widely accepted that a neurochemical imbalance underlies the pathophysiology of mood disorders. However, recent studies demonstrate that structural alterations also occur in response to stress and in patients with mood disorders [4,5,9]. Moreover, studies demonstrate that these structural alterations are reversible upon administration of antidepressants.

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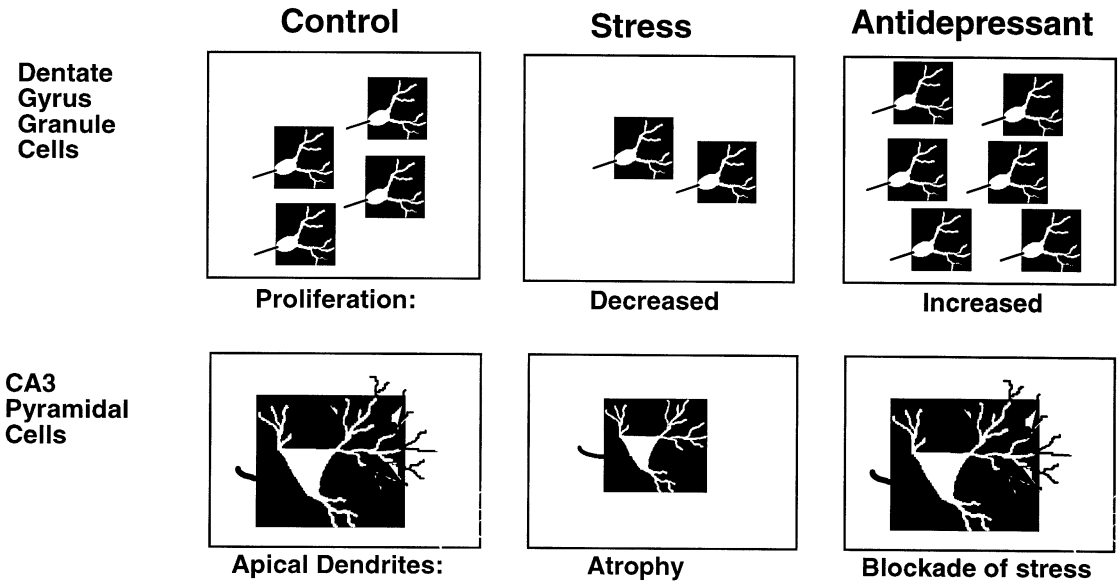

Fig. 1. A model of the structural alterations observed in the hippocampus. Stress can produce structural changes in both the granule cell layer and CA3 pyramidal cell layers of the hippocampus. Stress decreases cell proliferation in the granule cell layer and causes atrophy of the apical dendrites of CA3 pyramidal neurons. In contrast, antidepressant treatment increases cell proliferation and can block the atrophy of CA3 neurons.

Neuronal atrophy and loss in mood disorders

Studies in rodents and nonhuman primates demonstrate that exposure to stress can cause alterations in the processes or number of neurons. Repeated stress is reported to cause atrophy of CA3 pyramidal neurons in the hippocampus, including a decrease in the number and length of apical dendrites (*Fig. 1*) [10]. In addition, exposure to acute stress decreases the proliferation of cells in the dentate gyrus of the hippocampus [6]. The hippocampus is one of the few regions of the brain where neural progenitor cells continue to divide and give rise to new neurons in adult animals. In addition to these preclinical reports, brain imaging studies demonstrate that the volume of the hippocampus is decreased in patients with depression or posttraumatic stress disorder [12]. There are also reports of alterations in the cerebral cortex of patients with depression or bipolar disorder. These include a decrease in the volume of the subgenual prefrontal cortex and a decrease in the number of neurons and glia [3,11]. Future studies will be required to determine how frequently structural alterations are observed in mood disorders and if they are state or trait markers.

The atrophy and loss of neurons in the hippocampus, as well as cerebral cortex, could result from a number of factors (*Fig. 1*). This could include hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, glutamatergic excitoxicity, viral or bacterial infection, excitoxins, hypoxia-ischemia, or vulnerability to stress or other insults as a result of genetic background [4,5]. Although mild or moderate exposure to any of these factors alone may not be sufficient to cause structural and behavioral alterations, the cumulative effects over time could underlie the individual variability in stress responsiveness.

Action of antidepressant treatment

In contrast to atrophy and cell loss, antidepressant administration is reported to either block or produce effects that oppose the actions of stress. Administration of the antidepressant tianeptine is reported to block the atrophy of CA3 pyramidal neurons in response to long-term stress [5,10]. This effect was not observed with the 5-hydroxytryptamine (5-HT) selective reuptake inhibitor fluoxetine. Moreover, recent reports demonstrate that antidepressant administration

increases the proliferation of granule cells in the hippocampus [5,7,8]. Upregulation of cell proliferation has been observed with several different classes of antidepressants, including norepinephrine and 5-HT selective reuptake blockers, indicating that it may be a common action of antidepressants. In addition, this effect was dependent on chronic treatment, consistent with the time course for the therapeutic action of antidepressants. Antidepressant treatment is also reported to block the downregulation of neurogenesis that occurs in response to stress [9].

These studies suggest that upregulation of neurogenesis could oppose the effects of stress and reverse the hippocampal atrophy that has been reported in depressed patients. However, it is also possible that atrophy of CA3 pyramidal neurons contributes significantly to the reduced hippocampal volume. Additional postmortem studies are needed to determine whether one or both of these mechanisms contribute to the structural alterations that are observed in the hippocampus.

MOLECULAR DETERMINANTS OF NEURONAL PLASTICITY

Advances made in the study of learning and memory demonstrate a role for specific gene transcription factors and neurotrophic factors. This includes the cyclic adenosine monophosphate (cAMP) response element binding protein (CREB) and brain-derived neurotrophic factor (BDNF). Recent studies demonstrate that these same pathways are also altered by stress and antidepressant treatment.

Role of CREB in mood disorders

In addition to its regulation by the cAMP cascade, other signal transduction pathways also activate CREB. These include Ca^{2+}-calmodulin-dependent kinase, protein kinase C, and ribosomal S6 kinase, as well as cAMP-dependent protein kinase [5]. CREB may thereby serve as a central integrator of signaling for a number of extracellular stimuli that influence neuronal plasticity, as well as neuronal survival. We have found that the function and expression of CREB is upregulated by chronic antidepressant treatment, including norepinephrine and 5-HT selective reuptake inhibitors (*Fig. 2*) [5]. We have also found that viral-mediated expression of CREB in the hippocampus produces an antidepressant-like effect in behavioral models of depression, including the forced swim and learned helplessness paradigms [1]. Finally, a recent study has reported that levels of CREB are decreased in the cerebral cortex of depressed patients, but increased when patients were receiving antidepressant medication at the time of death [2]. These findings suggest that downregulation of CREB could contribute to the pathophysiology of depression and that upregulation of this transcription factor could contribute to the therapeutic response. Additional postmortem studies will be required to test this hypothesis.

Role of BDNF in depression

Neurotrophic factors, including BDNF, nerve growth factor, and neurotrophin-3, were originally characterized for their actions during the development and maturation of neurons. However, these neurotrophic factors are also expressed in the adult brain and are known to influence the survival and function of mature neurons. Moreover, neurotrophic factor expression is highly regulated by a variety of stimuli. These include stress and psychotropic drugs. The expression of BDNF in the hippocampus is dramatically downregulated by exposure to stress [15]. This effect is seen in the dentate gyrus, CA3 and CA1 pyramidal cell layers and is observed after acute or chronic stress. It is possible that the downregulation of BDNF may contribute to the atrophy of CA3 neurons and reduced neurogenesis of granule cells in the hippocampus, although elevated levels of adrenal glucocorticoids could also account for these effects.

In contrast to the effects of stress, chronic antidepressant administration increases the expression of BDNF in the hippocampus, as well as frontal cortex [4,5]. Induction of BDNF in the hippocampus is observed with different classes of antidepressants, but not with nonantidepressant psychotropic drugs, demonstrating the pharmacological specificity of this effect. In addition, antidepressant treatment blocks the downregulation of BDNF in response to stress. The possibility that upregulation of BDNF contributes to the therapeutic action of antidepressants is supported by behavioral studies. Chronic infusion of BDNF into the midbrain produces an antidepressant effect in the forced swim and learned helplessness models [14]. We have also found that a single infusion of BDNF into the hippocampus produces a potent and long-lasting antidepressant effect in these behavioral models [13]. Additional studies will be required to determine the significance of

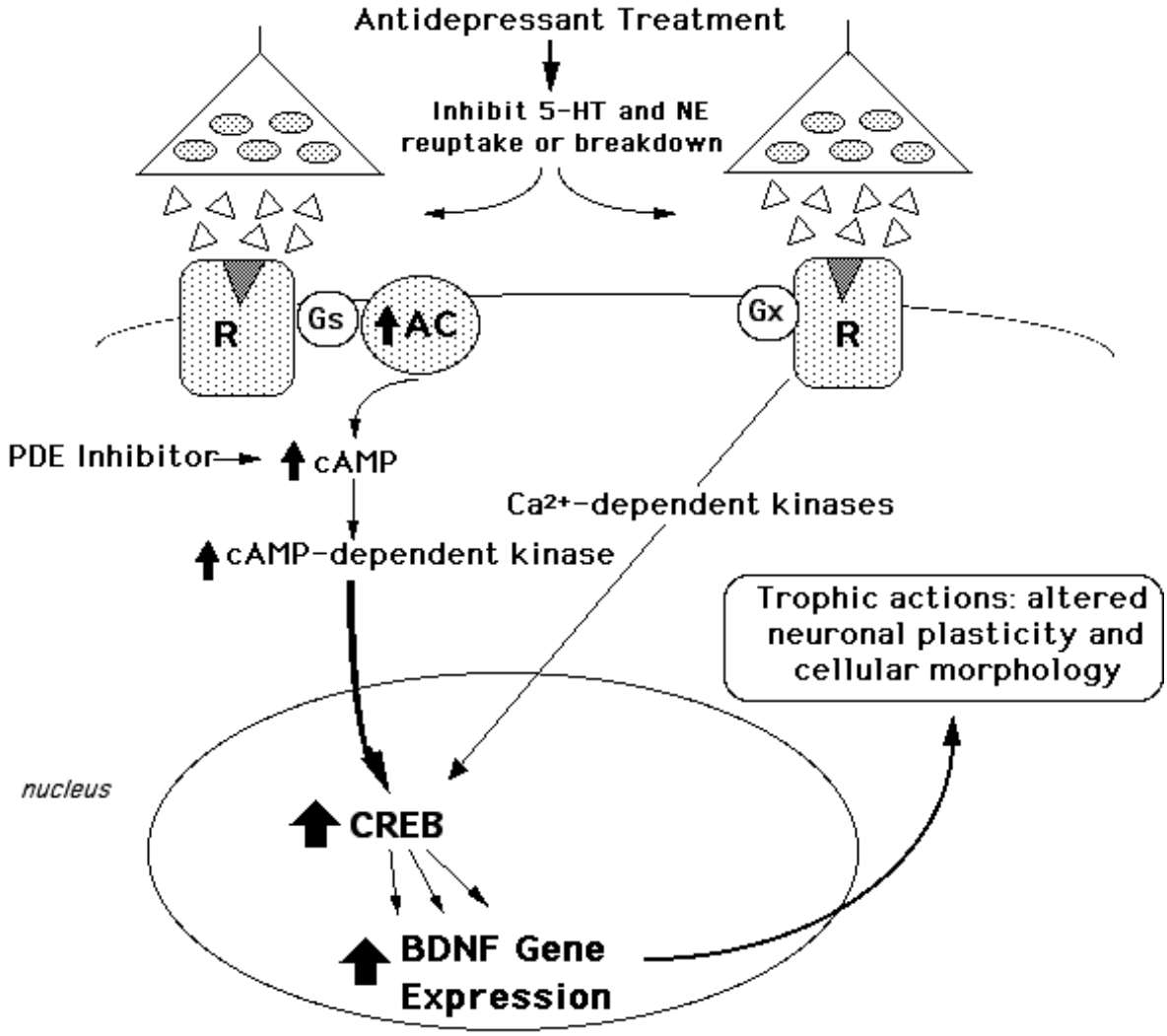

Fig. 2. Regulation of the cyclic adenosine monophosphate (cAMP)-response element binding protein (cAMP-CREB) cascade and expression of brain-derived neurotrophic factor (BDNF) by antidepressant treatment. Antidepressant treatment is reported to upregulate the cAMP-CREB cascade, including increased adenylyl cyclase (AC), upregulation of cAMP-dependent protein kinase, and increased function and expression of CREB. CREB can also be regulated by Ca^{2+}-dependent protein kinases. Activation of neurotransmitter receptors (R) can lead to regulation of the cAMP or Ca^{2+} signaling pathways. One of the genes regulated by the cAMP-CREB cascade and antidepressant treatment is BDNF. Upregulation of CREB and BDNF could contribute to the trophic effects of antidepressants, including synaptic remodeling and increased neurogenesis. 5-HT: 5-hydroxytryptamine; NE: norepinephrine; PDE: phosphodiesterase.

BDNF in mood disorders, including postmortem studies of BDNF levels in limbic brain regions.

PERSPECTIVES

The overview of studies outlined in this paper highlights significant conceptual advances for understanding the pathophysiology and treatment of mood disorders. This includes the astonishing discoveries that the shape and number of neurons can be altered in the adult brain. Moreover, the structural alterations that are caused by stress and that are observed in the brains of depressed patients are reversible, as observed with antidepressant medications. Elucidation of the signal

transduction pathways and gene transcription factors that underlie the actions of stress and antidepressants could also reveal targets for the development of novel therapeutic agents. The continued application of major advances in molecular and cellular neurobiology to psychiatric problems over the coming years holds a bright future for the treatment, and possibly prevention, of depression and other mood disorders.

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