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Neurotrophic factors and regulation of mood: Role of exercise, diet and metabolism

Ronald S. Duman *

Division of Molecular Psychiatry, Departments of Psychiatry and Pharmacology, Yale University School of Medicine, 34 Park Street, New Haven, CT 06508, USA

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Abstract

Results from basic and clinical studies demonstrate that stress and depression decrease neurotrophic factor expression and neurogenesis in brain, and that antidepressant treatment blocks or reverses these effects, leading to a neurotrophic hypothesis of depression. Neurotrophic factor expression and neurogenesis are also decreased during aging and could be risk factors for depression. In contrast, exercise and enriched environment increase neurotrophic support and neurogenesis, which could contribute to the blockade of the effects of stress and aging and produce antidepressant effects. A brief overview of this work and the specific neurotrophic factors involved are discussed in this review.

Keywords: Depression; Antidepressant; Stress; BDNF; Neurogenesis

1. Introduction

Over the years, depression research has focused on the regulation of serotonin and norepinephrine, particularly the synthetic enzymes and receptors that control these monoamine systems. However, more recent studies have identified relevant alterations of intracellular signal transduction pathways and target genes that contribute to the pathophysiology and treatment of depression. Studies of neurotrophic factors and neurogenesis have been of particular interest and have lead to a neurotrophic hypothesis of depression [9,10]. These studies demonstrate that stress and depression decrease neurotrophic factor levels and neurogenesis, resulting in structural abnormalities in animal models and depressed subjects. Aging also leads to decreased levels of neurotrophic factors and neurogenesis, which could contribute to risk of depression in elderly subjects. In contrast, antidepressant treatment produces opposite effects, and can block or reverse the effects of stress and depression.

In light of these studies it is notable that exercise and diet can also induce neurotrophic and neurogenic effects that have multiple beneficial actions on neuronal function and behavior. This review provides a brief overview of the literature and a discussion of the complex interactions between stress, exercise, diet and mood and the role of neurotrophic/growth factors in the regulation of normal and abnormal physiological processes.

2. Stress and depression decrease neurotrophic support and cause neuronal atrophy and cell loss

2.1. Stress decreases neurotrophic factor levels

Studies demonstrating that stress causes atrophy and cell loss of certain limbic brain structures, particularly the hippocampus [28,40], stimulated investigations of the nerve growth factor family, which includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF) and neurotrophin-3 (NT3). These factors play an important role in the development of the nervous system, but are also involved in the maintenance and survival of neurons in the adult brain. Moreover, the expression of these factors is activity-dependent and plays an important role in neuronal adaptation and neural plasticity (Fig. 1).

* Tel.: +1 203 974 7726; fax: +1 203 974 7724.
E-mail address: ronald.duman@yale.edu.

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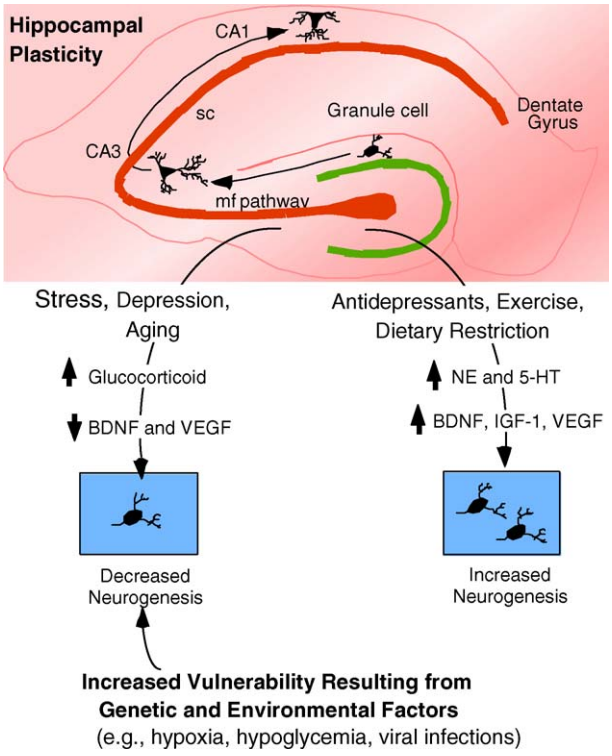

Fig. 1. A model demonstrating the opposing actions of stress/depression and antidepressants on hippocampal plasticity. The influence of aging, exercise and dietary restriction are also indicated. See text for further description and details.

Early studies demonstrated that stress results in a rapid and robust down-regulation of BDNF in the major subfields of the hippocampus [9]. Several different types of stress decrease the expression of BDNF, including immobilization, chronic unpredictable stress, swim stress, footshock, and early maternal deprivation. Expression of BDNF is also decreased during aging [26]. Although the mechanisms underlying the down-regulation of BDNF have not been fully characterized, elevated levels of adrenal-glucocorticoids appear to play a significant role.

In addition to BDNF, stress regulates the expression of other neurotrophic factors, including vascular endothelial growth factor (VEGF). VEGF regulates endothelial cell proliferation and angiogenesis, but also has neurotrophic, neuroprotective, and neurogenic effects. A recent study has demonstrated that exposure to chronic unpredictable stress decreases VEGF expression in the granule cell layer and hilar regions of the hippocampus [17]. The regulation of VEGF, as well as BDNF, may contribute to the influence of stress on adult neurogenesis and behavior (see below).

2.2. Levels of BDNF are decreased in depressed patients

The relevance of the basic research work is provided by studies of BDNF in depressed patients. Postmortem studies demonstrate that levels of BDNF in the hippocampus or prefrontal cortex are decreased in depressed suicide subjects relative to matched controls [11,20]. Studies of serum also demonstrate decreased levels of BDNF in depressed patients [19,45]. Although there are limitations to these postmortem and serum studies, these findings are consistent with the hypothesis that down-regulation of BDNF can contribute to the pathophysiology of depression.

2.3. Stress decreases neurogenesis

The hippocampus is one of two neurogenic zones in the adult brain. Neural progenitor cells in the subgranular zone divide and give rise to cells that differentiate and mature into neurons that migrate into the granule cell layer of the hippocampus [15,51]. Moreover, the rate of proliferation and survival of newborn cells can be regulated by a variety of environmental, endocrine, and neurobiological stimuli (Fig. 1).

In this regard, exposure to stress decreases the number of newborn neurons in the granule cell layer of adult hippocampus [10,28]. Different types of stress are reported to decrease adult neurogenesis, including intruder stress, predator stress, maternal separation, chronic mild stress, and footshock. Neurogenesis is also decreased during aging [26]. Mechanisms underlying the down-regulation of neurogenesis involve elevated levels of adrenal glucocorticoids, as well as decreased levels of BDNF and VEGF [10].

2.4. Stress and depression cause neuronal atrophy

The influence of stress on the morphology of neurons in the hippocampus has also been studied. McEwen and co-workers have demonstrated that exposing animals to repeated restraint stress (18 days) results in atrophy or remodeling of neurons in the hippocampus [28,29,53]. Results from postmortem studies also suggest that there is atrophy of hippocampal neurons in depressed patients. Morphometric analysis of the hippocampus of depressed patients demonstrates that there is a decrease in the size of granule cells and an increase in the packing density of these neurons [48], suggesting that there is a decrease in neuronal processes or neuropil in depressed subjects. The reduction in the number of processes combined with the reduced neurogenesis could contribute to the decreased hippocampal volume that has been observed in depressed patients (see below).

2.5. Volume of hippocampus is decreased in depressed patients

The results of basic research studies are also supported by brain imaging studies of depressed or PTSD patients which demonstrate a significant reduction of the volume of the hippocampus [2,41,43,44]. In addition to hippocampus, there are reports of decreased volumes of the prefrontal cortex and the amgydala brain regions linked to altered mood, anxiety, and cognition in depressed patients [9,42]. Taken together, these imaging studies provide direct evidence of decreased