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The Role of Brain-Derived Neurotrophic Factor in Depression

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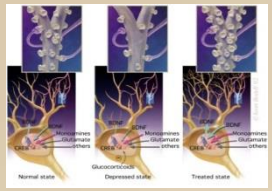
INTRODUCTION

According to The World Health Organization, depression is the fourth leading cause of total disease burden and the leading cause of disability worldwide. In the United States, results from the National Health and Nutrition Examination Survey reflect a 16.2% lifetime depression prevalence. Symptoms of depression can range from mild to severe and can be episodic or chronic. Depression has a high rate of comorbidity with multiple chronic diseases and other mental health disorders, predominately anxiety. Unfortunately, few Americans diagnosed with depression actually receive sufficient treatment and symptom management. Previous research has shown that individuals are more likely to seek treatment for depression in a primary care setting than a mental health specialty clinic, especially individuals of ethnic and racial minority populations. Approximately 50% of individuals suffering from depression are receiving no pharmacological or psychotherapeutical services (Shim, Baltrus, Ye, & Rust, 2011). Current research is investigating the role of brain-derived neurotrophic factor (BDNF) and the hypothalamic-pituitary-adrenal axis (HPA), and its role in the diagnosis, progression, and treatment of depression (U.S. National Library of Medicine [NLM], 2000, para. 2). This research provides insight into the mechanism of action of antidepressant medications and expands the available knowledge to facilitate more thorough patient education regarding the benefits of treatment.

Bacha, E. (2012). Depression in Men [Photograph]. Retrieved from http://enahams38.blogspot.com/2012/09/depression-in-men.html



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PATHOLOGICAL PROCESS

According to The World Health Organization, depression is the fourth leading cause of total disease burden and the leading cause of disability worldwide. In the United States, results from the National Health and Nutrition Examination Survey reflect a 16.2% lifetime depression prevalence. Symptoms of depression can range from mild to severe and can be episodic or chronic. Depression has a high rate of comorbidity with multiple chronic diseases and other mental health disorders, predominately anxiety. Unfortunately, few Americans diagnosed with depression actually receive sufficient treatment and symptom management. Previous research has shown that individuals are more likely to seek treatment for depression in a primary care setting than a mental health specialty clinic, especially individuals of ethnic and racial minority populations. Approximately 50% of individuals suffering from depression are receiving no pharmacological or psychotherapeutical services (Shim, Baltrus, Ye, & Rust, 2011). Current research is investigating the role of brain-derived neurotrophic factor (BDNF) and the hypothalamic-pituitary-adrenal axis (HPA), and its role in the diagnosis, progression, and treatment of depression (U.S. National Library of Medicine [NLM], 2000, para. 2). This research provides insight into the mechanism of action of antidepressant medications and expands the available knowledge to facilitate more thorough patient education regarding the benefits of treatment.

UNDERLYING PATHOLOGY

The neurobiology mechanisms of depression are not well known but are hypothesized to be a combination of genetic and environmental factors. For the past fifty years the Monoamine Hypothesis of Depression has been the leading explanation. This hypothesis is based on a deficit or imbalance of monoamine neurotransmitters; norepinephrine, serotonin, and dopamine. The enhancing effects of antidepressants on the monoaminergic system provides the primary support for this hypothesis. Clinical response to antidepressants only occurs after weeks to months of treatment and only chronic use is effective. This phenomenon suggests that lasting changes in gene expression are required for antidepressants efficacy (Masi & Brovedani, 2011). Research within the last decade has expanded the earlier Monoamine Hypothesis to integrate the gene transcription element which has been found to play a critical role in the diagnosis and treatment of depression. The Monoamine Hypothesis of Gene Expression has pointed to the role of neurotrophic factors, particularly brain-derived neurotrophic factor. The Neurotrophic Hypothesis of Neuronal Development further explores the role of BDNF in neuronal development, plasticity, and survival (Aricioglu & Gumru, 2012).

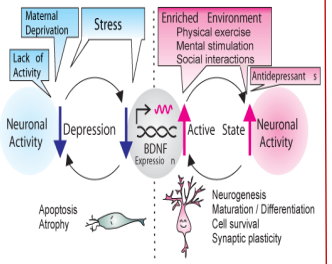
BDNF is initially synthesized as a precursor (prepro-BDNF) which then cleaves to pro-BDNF and the mature form of BDNF (mBDNF). mBDNF then binds with two different receptors at the target cell, TrkB and p75. mBDNF's trophic effects are mediated by TrkB receptor activation which is involved with promoting synaptic plasticity and regulating protein synthesis-dependent long-term potentiation, while pro-BDNF binds with high affinity to p75 receptors which are linked to the induction of apoptosis (Hill, 2012).

BDNF is present in multiple tissues and cell types; skeletal muscles, kidneys, retinas, motor neurons, the prostate, and the central nervous system. The highest concentration of BDNF is found in the dentate gyrus of the hippocampus, the cerebral cortex, and the basal forebrain. The majority of neurons are formed prenatally but parts of the adult brain, particularly the hippocampus and the olfactory bulb, retain the ability to grow new neurons from neural stem cells, neurogenesis. BDNF is one of the most active neurotrophins involved in stimulating and controlling neurogenesis. Patients with depression are found to have a reduction of hippocampal volume, decreased BDNF expression, and thus decreased neurogenesis (Masi & Brovedani, 2011).

It is unclear whether reduced hippocampal volume is a result of depression or a cause but growing research supports a direct link between decreased BDNF and depression. One of the hypothetical frameworks which links decreased BDNF with depression is the Hypothalamic-Pituitary-Adrenal Axis Abnormalities and Brain-Derived Neurotrophic Factor Hypothesis. This hypothesis provides further insight into the environmental factors involved in depression. Acute and chronic stress can induce hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis with a resultant increase in glucocorticoid levels which reduces the expression of BDNF and interferes with its binding to the TrkB receptor, thus decreasing BDNF signaling. The HPA axis is regulated via a negative feedback loop, increased glucocorticoids in the bloodstream cause an inhibitory response in the hypothalamus and the pituitary gland which decreases the synthesis of corticotropin releasing hormone and adrenocorticotropic hormone. The hippocampus also plays a role in this negative feedback loop by signaling the HPA axis to down-regulate cortisol production. The hippocampus has a high density of glucocorticoid receptors and increased cortisol levels have been shown to lead to neurotoxicity in this area. This perpetuates a vicious cycle of continual HPA axis hyperactivation and hippocampal damage (Kunugi, Hori, Adachi, & Numakawa, 2010).

SIGNIFICANCE OF PATHOLOGY

Research has found that BDNF expression in the hippocampus is increased with chronic and not with acute antidepressant treatment (Kunugi et al., 2010). BDNF levels are decreased in patients with depression and also correlate with the severity of the depression. BDNF levels after chronic antidepressant treatment increase to the same level found in healthy, non-depressed individuals. Due to the central role of BDNF in depression, health care providers may opt to obtain baseline BDNF levels prior to and throughout treatment to determine efficacy (Kurita, Nishino, Kato, Numata, & Sato, 2012). Gender specific considerations may also warrant further investigation, estrogen receptors co-localize with BDNF-synthesizing neurons and induce BDNF expression therefore, females with estrogen deficiencies or of post-menopausal age may present uniquely (Kunugi et al., 2010). Additional therapies that have been reported to increase BDNF levels are; zinc supplementation, omega-3 fatty acids, regular exercise, and caloric restrictions (Ranjbar et al., 2014). The HPA-BDNF link also provides useful insights into the benefits of stress reduction in the treatment of depression, thus regular exercise may serve a dual purpose in increasing BDNF and decreasing stress. Psychotherapy and a daily relaxation regimen can also be very useful as adjunct therapies.



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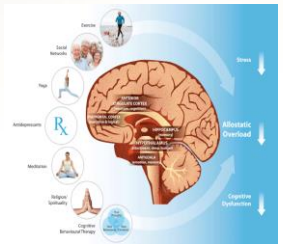
IMPLICATIONS FOR NURSING CARE

Educate Patients Regarding:

- The importance of antidepressant medication compliance and continual treatment
- The dual benefits of regular exercise
- The benefits of a healthy diet within an appropriate caloric range
- The role stress plays in depression and the benefits of adding a form of relaxation therapy to their daily routine
- The basic pathological process involved in depression to assist the patient with better understanding of the disease process and appropriate coping mechanisms



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CONCLUSION

The pathophysiology of depression plays an integral role in explaining the efficacy of treatment and additional physiological mechanisms that may be involved. The effects of BDNF levels in depressed patients may provide resources for additional screening tests, diagnostic tests, and tests for monitoring treatment efficacy. The HPA axis functionality may also provide additional testing tools to determine what role stress, current or past, is contributing to the patients disease process. Lastly, the inclusion of education regarding symptoms, contributing factors, additional therapies, and lifestyle modifications may lead to better disease management.

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