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The Neurobiology of Depression

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The Neurobiology of Depression

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Introduction

Major Depressive Disorder (MDD), also known as Major Depression, is a psychiatric syndrome characterized by pervasive disturbances in mood, sleep, appetite, energy, motivation, hedonic capacity and thinking. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), a depressive episode must be diagnosed if a patient has had depressed mood, or has lost interest or pleasure in most activities, for a duration of at least two weeks. However, depressive episodes often last months, sometimes years, and they carry a significant impairment in social and occupational functioning. Depressive episodes also tend to be recurrent and, if left untreated, most patients will have multiple episodes during their lifetime. The episodes tend to become more frequent and/or more severe as the disease progresses.

At least 5 of the following symptoms have been present during the same two-week period and represent a change from previous functioning

1. Depressed mood most of the day, nearly every day
2. Markedly diminished interest or pleasure in all, or almost all, activities
3. Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt
8. Diminished ability to think or concentrate, or indecisiveness
9. Recurrent thoughts of death, recurrent suicidal ideation, or a suicide attempt or a specific plan for committing suicide

MDD is a common medical disorder, with a lifetime prevalence of 17.1% and a 12-month prevalence of 10.3% in the general population. However, the prevalence of MDD in medical populations is even higher, with rates ranging from 30% to 50%, depending on the specific medical condition. This psychiatric disorder also carries a significant morbidity and mortality with a negative impact not only for the patient itself but for the family and for society in general. About two thirds of severely depressed patients exhibit suicidal ideation and 10% to 15% commit suicide.

The specific pathogenetic cause of depression is unknown but it is widely accepted that its etiology, course and long-term prognosis are influenced by genetic, environmental and neurobiological factors. Although many neurotransmitters and neurohormones have been linked to the pathophysiology of depression (e.g., norepinephrine, dopamine, thyroid hormones), research studies have implicated disturbances in the serotonin (5-HT) system and the Hypothalamic-Pituitary-Adrenal (HPA) axis, as well as interactions between the two systems.

That disturbances in the Hypothalamic-Pituitary-Adrenal axis and in serotonin may share a common pathophysiological mechanism is not surprising, since we know from animal studies that they interact extensively. These regions are also part of the limbic system, an area (including the hippocampus) implicated in the regulation of several vegetative functions (arousal, sleep, appetite and hedonic capacity) as well as in the control of mood. The recognition that the hippocampus is an integral component of the Hypothalamic-Pituitary-Adrenal axis has led some investigators to refer to this neuroendocrine system as the "Limbic"-Hypothalamic-Pituitary-Adrenal (LHPA) axis.

DOUBLE-BLIND TRIAL

Hot flashes in the menopause can usually be readily controlled by hormone replacement treatment with estrogen. However, there are some women who are unsuited to this approach, or simply want to have a non-hormonal treatment. A new drug, venlafaxine, has shown promise in reducing the frequency and intensity of hot flashes in a recent clinical study.

NEW CANCER MARKER DISCOVERED

A protein which interacts with the Huntington's disease gene product has proved to be a useful indicator of cancer progression.

The LHPA is the classic neuroendocrine system that responds to stress. Perception of stress by an organism results in a series of events, the final result of which is the secretion of glucocorticoids (cortisol in humans, corticosterone in rats) from the adrenal cortex. Activation and termination of the adrenocortical stress response is critical for adaptation and survival. Inhibition of stress responsiveness is partly achieved by the binding of circulating glucocorticoids to specific cytoplasmic receptors in the hypothalamus, where they inhibit corticotropin releasing hormone (CRH) and, consequently, pituitary adrenocorticotropin (ACTH) secretion. Additional modulation of the system is apparently achieved in limbic structures, especially the hippocampus.

Hyperactivity of the LHPA axis is a well-documented phenomenon in MDD. This dysregulation is manifested, among other things, by cortisol hypersecretion, failure to suppress cortisol secretion after dexamethasone administration, exaggerated adrenal responses to endocrine challenges and blunted ACTH response to CRH administration. Post-mortem studies have also found evidence of chronic LHPA activation in suicide victims, such as adrenal hyperplasia, downregulation of CRH receptors and increases in proopiomelanocortin mRNA, the precursor for ACTH, in the pituitary.

Historically, the presence of LHPA overactivity in patients with depression was believed by many to be a "secondary" phenomena of the illness, reflecting either a central monoaminergic disturbance, the stress of the illness or both. However, over the past few years, it has become clearer that the LHPA abnormalities in MDD are intimately linked to the pathophysiology of the disease. This change in perspective was stimulated, in part, by the increased awareness that glucocorticoids, the final products of the LHPA axis, have been shown to have profound effects on mood and behavior. For example, a high incidence of depression is linked to pathologies involving elevated corticosteroid levels, such as Cushing's syndrome. This corticosteroid-induced depression usually disappears when corticosteroid levels return to normal. In fact, it has become increasingly clear from both animal and clinical studies that circulating glucocorticoid levels provide important hormonal control of affect, which may be mediated by steroid-induced modulation of central limbic circuitry.

Serotonin Receptors and Depression

The serotonin system has been widely investigated as a key element in the pathophysiology of depression and as a mediator of the therapeutic action of antidepressants. Although the 5-HT system has many components, the three 5-HT molecules believed to be most closely associated with the neurobiology of mood are the serotonin transporter (5-HTt), the serotonin 1a receptor (5-HT1a) and the serotonin 2a receptor (5-HT2a, formerly 5-HT2).

Most newer (as well as older) antidepressants inhibit the re-uptake of serotonin from the synapse and alter 5-HTt protein and mRNA levels. Animal studies have also demonstrated that chronic antidepressant administration affects the function and number of the 5-HT1a and 2a receptors. Many electrophysiological studies have shown that antidepressants "upregulate" or "sensitize" 5-HT1a function in the hippocampus, while at the same time they "down-regulate" or "desensitize" 5-HT1a function elsewhere.

The 5-HT2a receptor has also been shown to be affected by chronic antidepressant treatment. Most, but not all, studies have reported decreases in 5-HT2a binding in the prefrontal cortex after chronic antidepressant administration. The opposite changes (5-HT2a upregulation) are found in the prefrontal cortex of suicide victims. In addition, subjects with a history of MDD dying of natural causes have increases in 5-HT2a binding in the prefrontal cortex.

Another level of complexity is added by the fact that 5-HT and the LHPA axis interact, anatomically and functionally, at multiple levels. For example, pharmacological stimulation with 5-HT agents can activate ACTH and cortisol release.

Stress, Serotonin and the LHPA axis

Stress and depression have been linked in a variety of ways. For example, both physical and psychological stressors have been shown to be temporally (and, perhaps, causally) related to the onset of depressive episodes. Some studies have suggested that, at least for recurrent depression, stressful life events are more common in "non-endogenous depression." Other studies have found that stressful life events are significantly correlated even with the first episode of psychotic/endogenous depression.

Another important link between depression and stress is the fact that both the LHPA and 5-HT systems, in addition to being involved in the pathophysiology of depression, are, also, critical contributors to the neurobiology of stress. In the lab, we have used chronic unpredictable stress, a postulated animal model of depression, to investigate the parallel changes in 5-HT and LHPA systems. We expose rats to

different mild to moderate stressors everyday, therefore making the stress "unpredictable" from day to day. Rats that undergo this treatment show LHPA overactivity and increases in peripheral glucocorticoids, very similar to those found in MDD, as well as a significant decrease in 5-HT_{1a} mRNA and binding in the hippocampus and a significant increase in 5-HT_{2a} receptor and mRNA levels in the prefrontal cortex. As stated above, these "opposite" effects (hippocampal 5-HT_{1a} downregulation, cortical 5-HT_{2a} upregulation) are also found in suicide victims with a history of depression.

Antidepressant Medications, the LHPA Axis and 5-HT Receptors

The LHPA overactivity observed with chronic unpredictable stress can also be prevented by the chronic administration of either imipramine or desipramine, two tricyclic antidepressants. Both desipramine and imipramine also reverse the stress-induced downregulation of 5-HT_{1a} in hippocampus, and the 5-HT_{2a} upregulation in cortex. On the other hand, zimelidine and fluoxetine, two specific serotonin reuptake inhibitors, are unable to prevent the stress-induced elevation in corticosterone levels. This failure to prevent the LHPA overactivity is associated with a failure to restore the 5-HT receptor changes to baseline levels. This suggests that failure of an antidepressant to reverse the LHPA hypersecretion is associated with a failure to prevent the 5-HT receptor "dysregulation" secondary to chronic stress. We have proposed that this may be one of the neurobiological mechanisms underlying "treatment resistance" in patients with severe depression.

There is some clinical evidence that these mechanisms may be operating in depressive disorders. Persistence of hypercortisolemia after antidepressant administration in depressed patients has been associated with relapse and poorer treatment outcome. In addition, some clinical studies have found that tricyclics are more effective than SSRIs in the treatment of melancholia. Venlafaxine, an antidepressant with both norepinephrine and 5-HT reuptake activity, was reported to be more effective than fluoxetine in treating melancholic depression. Since melancholia and severity of depression are associated with a higher incidence of hypercortisolemia, it is possible that the presence of a severely disturbed LHPA axis in this population may be contributing to the relative resistance to SSRI treatment. Interestingly, many augmentation strategies in treatment resistant patients are, in effect, attempts to broaden the biochemical profile of the pharmacological treatment, which may be more effective in reversing LHPA overactivity than a treatment whose main impact is in a single neurotransmitter system.

A Model of the Interplay Between Stress, the LHPA Axis, Serotonin and Antidepressants

Based on the animal and human studies reviewed here, we can generate a working model of the interplay between stress, the LHPA axis, 5-HT receptors and their potential interactions in suicide and depression:

- 1) Depressed patients, as well as suicide victims, show evidence of overactivity of the LHPA axis.
- 2) Chronic stress and/or high steroid levels in rats result in an alteration of specific 5-HT receptors (e.g., increases in cortical 5-HT_{2a}, decreases in hippocampal 5-HT_{1a}).
- 3) Many human studies show the same receptor changes in the brain of suicide victims (increases in cortical 5-HT_{2a}, decreases in hippocampal 5-HT_{1a}) as found in hypercortisoid states.
- 4) Chronic antidepressant administration causes opposite 5-HT receptor changes to those seen with chronic stress.
- 5) Antidepressant administration reverses the overactivity of the LHPA axis.

Conclusion

Corticosteroid modulation of 5-HT receptors has important implications for the pathophysiology and treatment of mood disorders and, perhaps, suicide. This may be one of the mechanisms by which stressful events can precipitate depressive episodes in some (genetically) vulnerable individuals and or precipitate suicidal behavior. Another implication is that altered 5-HT levels or metabolism do not necessarily have to be present for 5-HT receptor abnormalities to occur. Based on the animal data, it is apparent that specific 5-HT receptors may be directly regulated in response to alterations of corticosteroid levels. An important therapeutic implication of this model is the prediction that agents which can reduce the stress response and/or decrease LHPA activation will be useful in the pharmacological treatment of anxiety, depression and, perhaps, suicidal behavior.

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Source

- Juan F. López, M.D., *The Neurobiology of Depression*, <http://www.cyberounds.com>

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