bm.genomicpress.com

Brain Medicine

OPEN

VIEWPOINT

Is depression a neuroendocrine disease?

Brain Medicine; https://doi.org/10.61373/bm024v.0106

Keywords: Corticotropin-releasing hormone, inflammation, melancholic depression, neuroendocrine dysfunction, neuroplasticity, stress

Depression, according to the World Health Organization, stands as one of the most impactful disabilities worldwide. Its toll reaches beyond mood and thought, extending into physical health risks like coronary artery disease, diabetes, osteoporosis, and stroke, leading to a lifespan reduction of approximately 7 to 10 years in those affected. This paper explores the view of depression as a neuroendocrine disorder, especially focusing on the subtype of melancholic depression. Structural and functional disruptions in brain areas—such as the prefrontal cortex and hippocampus—reveal a misalignment in the stress response system that might drive depressive symptoms. Specifically, the roles of corticotropin-releasing hormone, norepinephrine hyperactivity, glucocorticoid levels, and inflammation-related mechanisms are investigated here. These insights point to promising new treatments targeting these neuroendocrine pathways that may enhance therapeutic responses.

Introduction

Depression's role as a global health burden is well established; it ranks as the world's leading cause of disability. However, its impact reaches far beyond mental well-being, affecting physical health in ways that can be devastating. Patients with depression face an elevated risk of early-onset coronary artery disease, diabetes, osteoporosis, and even stroke, collectively shortening life expectancy by about 7 to 10 years. Interestingly, the very biological mechanisms responsible for the emotional toll of depression seem to contribute to these physical ailments as well (1).

Neuroendocrine changes are commonly observed in depression, notably in peripheral endocrine function, which frequently mirrors the broader disruptions within the neuroendocrine system (1).

Melancholic Depression: A Distinct Subtype

Melancholic depression represents a unique expression of the disorder. Unlike what many expect from depression, melancholia often brings not sluggishness but heightened self-directed anxiety, vigilance, and feelings of extreme worthlessness. Common features include anhedonia, insomnia, and hopelessness, particularly pronounced in the morning—a time when symptoms are often at their worst. Elevated activity in systems like the corticotropin-releasing hormone (CRH), the HPA axis, and the sympathetic nervous system support the idea that melancholia involves an overactive stress response (2).

Those with melancholic depression often find their focus glued to negative or distressing thoughts, an effect exacerbated by elevated noradrenergic activity and higher cortisol levels, creating a mental environment that's hard to break free from (3).

Neurobiological Roots: Volume, Neurogenesis, and Synaptic Health

There are notable structural changes in melancholic depression, such as a reduction of up to 40% in the volume of the subgenual prefrontal cortex—a critical regulator of the stress response. This loss affects neural plasticity, reduces synaptic protein availability, and weakens neural connections. The subgenual prefrontal cortex plays pivotal roles, from dampening amygdala-driven fear and anxiety to facilitating pleasure responses via the nucleus accumbens (4).

In addition to subgenual prefrontal cortex changes, the dorsolateral prefrontal cortex—which assists in emotional regulation and cognitive control—also shrinks, as does the left orbitofrontal cortex, impairing the brain's reward processing capacity. Lower burst firing in the habenula limits dopamine in the nucleus accumbens, making it difficult for individuals to experience pleasure (3, 5).

On the other hand, the amygdala—the region connected with fear and anxiety—swells in size and becomes hyperactive, intensifying the anxiety that defines melancholia. Conversely, the hippocampus shows significant shrinkage, impacting memory, learning, and HPA axis regulation, all of which exacerbate depressive symptoms (3).

Stress and Inflammation in Depression

Stress and inflammation are closely intertwined; one readily activates the other. In depressed individuals, this interplay can lead to a heightened inflammatory state affecting both the brain and peripheral systems (6). Cytokine levels rise, microglia become active, and the overall inflammatory load increases, suggesting that anti-inflammatory medications could complement traditional antidepressants (7, 8).

CRH, which is consistently elevated in melancholia, is a potent inflammatory molecule, creating a feedback loop that worsens depressive symptoms. In turn, inflammatory mediators stimulate CRH release, linking stress and immune responses to deepening depressive states (3).

The Role of Antidepressants

Many of the structural and functional issues associated with melancholia are reversible or modifiable with antidepressants, which aid in restoring hippocampal volume and improving subgenual prefrontal cortex integrity. This understanding helps refine treatment options, making them more effective (3).

Endocrine Contributions to Structural and Physiological Changes in Depression

CRH

CRH plays a significant role in driving the symptoms of melancholia, contributing to hyperarousal, anxiety, and activation of the HPA axis, which increases stress hormone secretion and triggers a proinflammatory state. Notably, CRH suppresses nonessential functions like sleep, appetite, and even sexual behavior—responses thought to have evolved as survival mechanisms in high-stress situations. Unfortunately, in depression, these effects are exaggerated and maladaptive (9, 10).

High levels of CRH can even have neurotoxic consequences, particularly in the hippocampus, where damage can deepen depressive symptoms and impair memory and learning (11).

Received: 29 July 2024. Revised: 26 September 2024 and 22 October 2024. Accepted: 25 October 2024.
Published online: 14 November 2024.

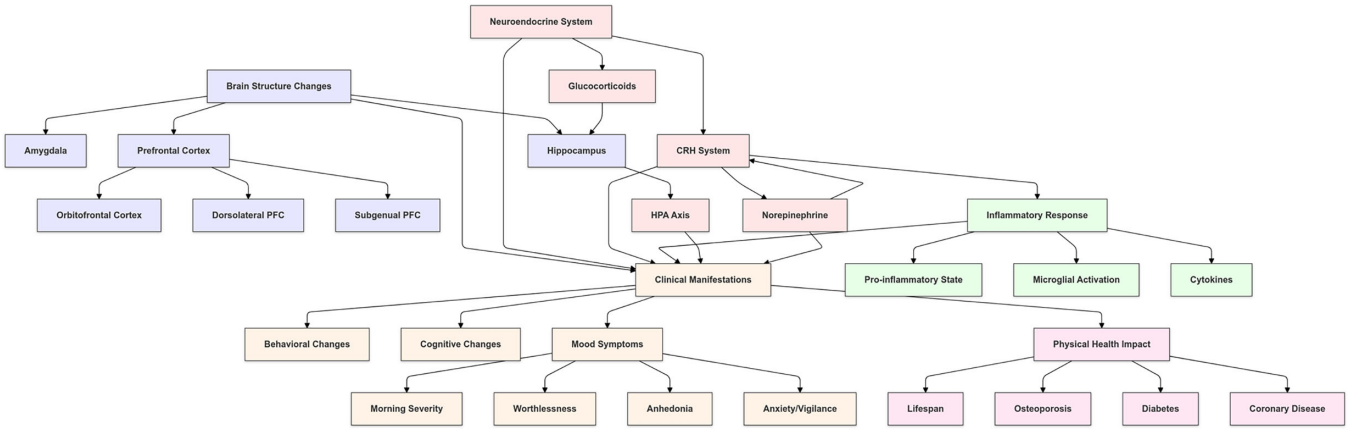

Figure 1. Depression as a neuroendocrine disease: Key pathways and clinical manifestations. This comprehensive diagram maps the critical interconnections between brain structure, neuroendocrine systems, and clinical manifestations in depression, with **bold text** emphasizing major components and their relationships. The pathways demonstrate how structural brain changes, neuroendocrine dysfunction, and inflammatory responses collectively contribute to both psychological symptoms and physical health impacts. Color coding represents distinct system components: light purple indicates brain structure changes and neural circuits, including **prefrontal cortex** regions and **limbic structures**; light red shows neuroendocrine system components, including **CRH, glucocorticoids**, and **HPA axis** activity; light green represents inflammatory pathways and immune responses, including **cytokines** and **microglial activation**; light orange depicts clinical manifestations including **behavioral**, **cognitive**, and **mood symptoms**; and light pink indicates physical health impacts including effects on **lifespan**, **osteoporosis**, **diabetes**, and **coronary disease**. The diagram shows how brain structure changes (particularly in the prefrontal cortex, hippocampus, and amygdala) interact with neuroendocrine disruptions, notably in the CRH system and glucocorticoid signaling. These systems form bidirectional relationships, as seen in the CRH-norepinephrine feedback loop. The inflammatory response system is activated by and influences these neuroendocrine changes. Together, these biological alterations underlie the clinical manifestations of depression, including both psychological symptoms (**mood changes**, **anhedonia**, **anxiety**) and physical health impacts. Key pathways highlight how glucocorticoids damage hippocampal tissue, the central role of CRH in activating both norepinephrine and inflammatory responses, multiple biological systems converging to produce clinical manifestations, and the direct connection between clinical symptoms and physical health outcomes. This integrative model emphasizes depression as a systemic disorder affecting both brain and body, with multiple interacting pathways contributing to its clinical presentation and health consequences.

Norepinephrine and the Sympathetic Nervous System

The CRH and locus-coeruleus-norepinephrine systems are tightly interlinked, each stimulating the other. Elevated norepinephrine levels have a range of effects, from increasing anxiety and arousal to fostering inflammatory responses. Additionally, norepinephrine appears to drive increased platelet activity and coagulation factor release, both of which can contribute to physical health issues associated with melancholia (12).

The combined effects of CRH, norepinephrine, cortisol, and inflammatory pathways help explain why depression often leads to early onset of various illnesses and a shortened lifespan for those affected (3, 13, 14).

Glucocorticoids

Known for their neurotoxic impact, glucocorticoids significantly contribute to hippocampal tissue loss observed in depressive patients. Studies show that when glucocorticoid effects are blocked, stress-induced tissue loss in the hippocampus is markedly reduced. Elevated glucocorticoids also increase CRH activity in the amygdala, amplifying stress responses and associated anxiety (3).

Insulin Signaling in the Brain and Peripheral Systems

Insulin plays a crucial role in neuroplasticity, particularly within the hippocampus, where it supports dendritic integrity and synaptic function. However, depression-related hyperinsulinism and elevated glucocorticoid levels can reduce insulin transport across the blood–brain barrier, potentially impairing cognitive resilience and further complicating the depressive state (15).

Sex Hormones and Depression

Estrogen and Related Compounds

Estrogen receptor beta agonists appear to promote synaptic health, enhancing cognitive function and alleviating depressive symptoms. Estradiol and some selective estrogen receptor modulators demonstrate neuroprotective effects, reducing inflammatory responses in glial cells, diminishing anxiety, and supporting synaptic plasticity within the hippocampus. This makes estrogenic compounds potential targets for innovative antidepressant therapies (16).

Androgens

Androgens, too, influence mood regulation through their effects on brain regions like the amygdala and prefrontal cortex. For instance, testosterone appears to modulate impulse control and aggression by reducing connectivity between the amygdala and the orbitofrontal cortex. Androgen deficiencies, particularly in males, are associated with reduced hippocampal volume, while androgen supplementation has shown promise in promoting hippocampal plasticity and improving memory functions (16).

Thyroid Hormones

Thyroid supplementation has long been used to boost responses to antidepressants. Hypothyroidism, commonly linked to increased amygdala activity, may be one factor in depressive symptoms. Thyroid hormones aid hippocampal neurogenesis, which is essential for mood stabilization and cognitive function (16).

Atypical Depression: A Contrast to Melancholia

Atypical depression contrasts markedly with melancholic depression, presenting with lethargy, hypersomnia, and increased appetite rather than anxiety and agitation. Unlike melancholia, atypical depression is characterized by lower CRH secretion and cortisol levels, suggesting a possible hypoactive stress response, which highlights the neuroendocrine variability within depressive subtypes (2, 3).

Conclusions

The neuroendocrine landscape of depression, particularly in cases of melancholia, offers a complex and nuanced picture of how hormonal and neurobiological systems contribute to the disorder. From alterations in brain structures like the prefrontal cortex and hippocampus to changes in hormonal activity involving CRH, norepinephrine, and glucocorticoids,

each component plays a role in shaping depressive symptoms and in contributing to the physical health manifestations of this disorder (see Figure 1). Innovative treatments targeting neuroendocrine dysfunction—such as CRH antagonists, IRS p53 agonists, glucocorticoid and mineralocorticoid receptor modulators, and estrogenic compounds—represent promising avenues for more effective management of depressive illness.

Acknowledgments

This paper is part of a special Festschrift issue of Brain Medicine commemorating the centennial of Dr. Seymour Reichlin's birth and celebrating his pioneering contributions to neuroendocrinology. Dr. Reichlin's remarkable career spanning nearly eight decades has fundamentally shaped our understanding of hypothalamic-pituitary regulation, neuroendocrine stress responses, and psychoneuroimmunology. His work as a researcher, clinician, mentor, and leader has influenced generations of endocrinologists worldwide.

Funding Sources

This article was not funded by external sources.

Author Disclosures

The author has confirmed that no conflict of interest exists.

Philip W. Gold[1]

[1] *Intramural Research Program, National Institute of Mental Health, Bethesda, Maryland 20892, USA*

✉ *e-mail: philipgold@mail.nih.gov*

References

1. Gold PW. Endocrine factors in key structural and intracellular changes in depression. Trends Endocrinol Metab. 2021;32(4):212–23. DOI: 10.1016/j.tem.2021.01.003. PMID: 33622587
2. Gold PW, Goodwin FK, Chrousos GP. Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress (1). N Engl J Med. 1988;319(6):348–53. DOI: 10.1056/NEJM198808113190606. PMID: 3292920
3. Gold PW. The organization of the stress system and its dysregulation in depressive illness. Mol Psychiat. 2015;20(1):32–47. DOI: 10.1038/mp.2014.163. PMID: 25486982
4. Drevets WC, Price JL, Simpson JR Jr., Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature. 1997;386(6627):824–7. DOI: 10.1038/386824a0. PMID: 9126739
5. Gold PW. Breaking Through Depression: A Guide to the Next Generation of Promising Research and Revolutionary New Treatments. New York, NY: 12 Hachette Book Group; 2023.
6. Han M-H, Nestler EJ. Neural substrates of depression and resilience. Neurotherapeutics. 2017;14(3):677–86. DOI: 10.1007/s13311-017-0527-x. PMID: 28397115; PMCID: PMC5509625
7. Cassarotto PC, Girych M, Fred SM, Kovaleva V, Moliner R, Enkavi G, et al. Antidepressant drugs act by directly binding to TRKB neurotrophin receptors. Cell. 2021;184:1299–313.e19. DOI: 10.1016/j.cell.2021.01.034. PMID: 33606976; PMCID: PMC7938888
8. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016;16(1):22–34. DOI: 10.1038/nri.2015.5. PMID: 26711676; PMCID: PMC5542678
9. Gold PW, Chrousos G, Kellner C, Post R, Roy A, Augerinos P, et al. Psychiatric implications of basic and clinical studies with corticotropin releasing factor. Am J Psychiat. 1984;141:619–27. DOI: 10.1176/ajp.141.5.619. PMID: 6324597
10. Gold PW, Loriaux DL, Roy A, Kling MA, Calabrese JR, Kellner CH, et al. Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease. Pathophysiologic and diagnostic implications. N Eng J Med. 1986;314(21):1329–35. DOI: 10.1056/NEJM198605223142101. PMID: 3010108
11. Gold PW, Wong ML, Goldstein DS, Gold HK, Ronsaville DS, Esler M, et al. Cardiac implications of increased arterial entry and reversible 24-h central and peripheral norepinephrine levels in melancholia. Proc Natl Acad Sci U S A. 2005;102(23):8303–8. DOI: 10.1073/pnas.0503069102. PMID: 15919819; PMCID: PMC1140482
12. Gold PW, Kadriu B. A major role for the lateral habenula in depressive illness: Physiologic and molecular mechanisms. Front Psychiatry. 2019;10:320. DOI: 10.3389/fpsyt.2019.00320. PMID: 31231247; PMCID: PMC6558383
13. Calogero AE, Gallucci WT, Chrousos GP, Gold PW. Catecholamine effects upon rat hypothalamic corticotropin-releasing hormone secretion in vitro. J Clin Invest. 1988;82:839–46. DOI: 10.1172/JCI113687. PMID: 2901433; PMCID: PMC303591
14. Wong ML, Kling MA, Munson PJ, Listwak S, Licinio J, Prolo P, et al. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. Proc Natl Acad Sci U S A. 2000;97(1):325–30. DOI: 10.1073/pnas.97.1.325. PMID: 10618417; PMCID: PMC26662
15. Gold PW, Licinio J, Pavlatou MG. Pathological parainflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, klotho and PPAR-γ systems. Mol Psychiatry. 2013;18(2):154–65. DOI: 10.1038/mp.2012.167. PMID: 23183489; PMCID: PMC10064987
16. Swaab DF, Bao AM, Lucassen PG. The stress system in the human brain in depression and neurodegeneration. Ageing Res Rev. 2005;4(2):141–94. DOI: 10.1016/j.arr.2005.03.003. PMID: 15996533