Research Open

Endocrinology, Diabetes and Metabolism Journal

Volume 8 Issue 1

Short Article

The Role of Endocrine Mediators in the Neurodegeneration and Synaptic Dysfunction of Depressive Illness

Philip W Gold M.D*

Office of the Scientific Director, 10 Center Drive, Intramural Research Program, NIH/NIMH, NIH Clinical Center 2D-46-1284, Bethesda, MD 20814-1284, USA

Corresponding author: Philip W Gold, Office of the Scientific Director, 10 Center Drive, Intramural Research Program, NIH/NIMH, NIH Clinical Center 2D-46-1284, Bethesda, MD 20814-1284, USA

Received: January 19, 2024; **Accepted:** January 25, 2024; **Published:** February 02, 2024

Major depression is the 2nd greatest cause of disability worldwide, and the first greatest cause in individuals under 45 years of age. It is a lifetime disorder with multiple depressive episodes interspersed by remissions. Its principal manifestations include anxiety, especially directed at the self, feelings of worthlessness, inability to anticipate or experience pleasure, significant changes in appetite and sleep, hypersecretion of cortisol and norepinephrine [1], and a highly significant increase in the incidences of complex medical illness such as coronary artery disease, stroke [2], diabetes [3], and osteoporosis [4]. Specific central nervous system loci have been connected to these stigmata. There is a. loss of 40% in the volume of the subgenual prefrontal cortex [5,6], making depression a neurodegenerative disease. This site estimates the likelihood of punishment or reward, helps set the tone for the level of self-esteem, ordinarily restrains the amygdala in its generation of fear, accentuates the activity of the nucleus accumbens reward and pleasure center, and restrains the activity of the CRH-cortisol system and the sympathetic nervous system [1]. Its deficits in depression contribute to the majority of its principal clinical manifestations. As noted, these include anxiety and feelings of worthlessness, the decreased activities of the nucleus accumbens and ventral striatal system reward and pleasure centers, as well as hypercortisolism and a hypernoradrenergic state [1].

Hormonal mediators play large roles in these clinical and biochemical manifestations [7]. Corticotropin releasing hormone plays a significant role in the overall biological stigmata of depressive illness. We showed that CRH was hypersecreted in depression [8]. It is predominantly located in the hypothalamus to stimulate the pituitary-adrenal axis and in the amygdala to activate the locus-ceruleus norepinephrine system. It is by itself neurotoxic, and one of its principal effects, the inducement of hypercortisolism also promotes neurodegeneration and maladaptive central nervous system activity. It is also a potent stimulus to inflammation, and its actions include promoting the degranulation of mast cells. Either psychological or emotional stress activates both the hypothalamic and amygdala components of the CRH system [8].

Stress also activates inflammation in the brain and periphery independent of CRH. Circulating inflammatory mediators also damage neural tissue and function and play a significant role in the stigmata of depression [9,10]. In our early evolutionary history, the primary stressors were serious: either competition for territory or competitions for mates. In these instances, even the perception of danger stimulated neuroinflammation, in part, as a premonitory response to support tissue repair in the face of a flight or fight situation.

Norepinephrine excess in depression [11,12] also has deleterious effects. It not only produces anxiety, but also increases heart rate and blood pressure, production of a proinflammatory state (synergistic with CRH) increased coagulation, and insulin resistance.

Insulin in brain derives from the periphery to activate a host of insulin receptors in sites that are involved in depressive pathophysiology. Insulin resistances in the periphery [9] associated with increased plasma insulin levels decrease insulin transport into the CNS by downregulating blood brain barrier insulin receptors. Insulin in brain supports the density of synapses, maintain synaptic itegrity, and synaptic density and integrity decrease when insulin receptors are removed or dysfunctional. Depression is associated with significant synaptic dysfunction in multiple ways [13].

Estrogen in females and androgens in male are often reduced in depression. Estrogen is neuroprotective, anti-inflammatory, reduces anxiety and depression, promote cognition, and modulate synaptic plasticity in rodents. Androgen deficiency is associated with depression which is corrected by restoring androgen levels to normal.

Thyroid hormones are often low in patients with depressive illness [14]. Thyroid hormones suppress the activity of the amygdala and thyroid deficiency is likely to promote anxiety. Adult hypothyroidism is associated with an increase in glucocorticoid actions in the amygdala, which we have shown promotes anxiety, is associated with fear memory enhancement, and deficits in the extinction of fear memories. These deficits are reversed by thyroid hormone replacement.

Concluding Remarks

Endocrine abnormalities contribute to the neurogenerative aspects of depressive illness, to synaptic abnormalities, and can adversely affect sites such as the amygdala and the ventral striatum. CRH, noradrenergic, and glucocorticoid antagonists and anti-inflammatory

treatment can all have therapeutic potential for treating depression. Agents that are neuroprotective can also have therapeutic potential in treating depression, and multiple neuroprotective compounds are currently in active trials in antidepressant protocols.

References

1. PW G (2015) The organization of the stress system and its dysregulation in depressive illness. *Mol Psychiat* 20: 32-47. [crossref]
2. Dong JY, Zhang YH, Tong J, Qin LQ (2012) Depression and risk of stroke: a meta-analysis of prospective studies. *Stroke* 43: 32-37. [crossref]
3. MJ K, JWR T, ATF B, RJ H, FJ S, F P (2005) Depression as a risk factor for the onset of type II diabetes. *Diabetologia* 49: 837-845. [crossref]
4. Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, et al. (1996) Bone mineral density in women with depression. *N Engl J Med* 335: 1176-1181. [crossref]
5. Drevets WC, Price JL, Simpson JR, Todd RD, Reich T, et al. (1997) Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386: 824-827. [crossref]
6. Drevets WC, Savitz J, Trimble M (2008) The subgenual anterior cingulate cortex in mood disorders. *CNS spectrums* 13: 663-681. [crossref]
7. PW G (2023) Breaking Through Depression: A Guide to the Next Generation of Promising Research and Revolutionary New Treatments. New York, NY: 12 Hachette Book Group; 2023.
8. Gold PW LL, Roy A, Kling MA, Calabrese JR, et al. (1986) Responses to corticotropin-releasing hormone iushing's disease. Pathophysiologic and diagnostic implications. *N. Eng. J. Med* 1329-1335. [crossref]
9. Miller AH, Raison CL (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat Rev Immunol* 16: 22-34. [crossref]
10. Miller AH, Maletic V, Raison CL (2009) Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* 65: 732-741. [crossref]
11. Gold PW, Wong ML, Goldstein DS, Gold HK, Ronsaville DS, et al. (2005) Cardiac implications of increased arterial entry and reversible 24-h central and peripheral norepinephrine levels in melancholia. *Proc Natl Acad Sci U S A* 102: 8303-8308. [crossref]
12. Wong ML, Kling MA, Munson PJ, Listwak S, Licinio J, et al. (2000) 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* 97: 325-330. [crossref]
13. Gold PW, Licinio J, Pavlatou MG (2013) Pathological parainflammation and endoplasmic reticulum stress in depression: potential translational targets through the CNS insulin, klotho and PPAR-γ systems. *Molecular Psychiatry* 18: 154-165. [crossref]
14. Bode H, Ivens B, Bschor T, Schwarzer G, Henssler J, et al. (2022) Hyperthyroidism and clinical depression: a systematic review and meta-analysis. *Transl Psychiatry* 12: 362. [crossref]

Citation:

Gold PW (2024) The Role of Endocrine Mediators in the Neurodegeneration and Synaptic Dysfunction of Depressive Illness. *Endocrinol Diabetes Metab J* Volume 8(1): 1-2.