

- Second Messenger -

Worried Sick: Antidepressants as Anti-Inflammatory Agents

Anxiety and depression: It's not just in your head

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receptors in the hypothalamus and pituitary. This feedback inhibition loop plays a critical anti-inflammatory role by turning off the stress response and stopping release of stress mediators (Figure 1).³

Paradoxically, pro-inflammatory cytokines and other humoral mediators of inflammation potently stimulate HPA axis and extra-hypothalamic CRF release. The resulting neural sensitization at multiple levels leads to amplification of the inflammatory response to each subsequent stressor.⁴ To make matters worse, pro-inflammatory cytokines antagonize GC receptor function, thereby interfering with the GC-mediated feedback inhibition necessary to shut off CRF release.⁵ With repeated or chronic stress, this self-promoting cycle makes it increasingly difficult to return to normal HPA axis functioning.

Persistent anxiety and depression are health risks

Inability to shut off the stress response disrupts the finely-tuned hypothalamic modulation of neuronal, neuroendocrine, and immune systems which function to protect our health in the short term.^{2,3} Prolonged or repeated activation of the stress axis ultimately results in a self-perpetuating cycle of enhanced stress reactivity and persistently increased inflammatory activity in chronically stressed, anxious, and/or depressed individuals. Beyond the contribution to neurodegenerative effects on key stress-mediating areas of the brain such as the hippocampus,⁶ loss of effective control of the stress enhances the development of a variety of medical disorders, including cardiovascular disease (atherosclerosis and coronary artery disease), metabolic disorders (insulin resistance, abdominal obesity, bone demineralization), immunologic dysfunction (susceptibility to infection, autoimmune disease), and neuroendocrine disorders.⁷⁻⁹

Worried sick

Is worrying itself actually harmful to your health? There is abundant clinical evidence that humans experiencing negative emotions or stress exhibit increased synthesis and release of proinflammatory cytokines.¹ This represents one possible mechanism by which depression may contribute to the acceleration of atherosclerosis and subsequent cardiovascular morbidity and post-myocardial mortality.⁷ Less widely known is that anxiety disorders confer the same risk as depression for cardiovascular morbidity and mortality.¹ Anxiety disorders also confer increased risk for other medical disorders. Harter and colleagues conducted

Issue Anxiety and depression predict poor health outcomes

Actions To consider evidence that anxiety and depression function like stress to promote distressing somatic symptoms and adverse health effects, and that the therapeutic effects of antidepressants include reduction in the release of pro-inflammatory cytokines

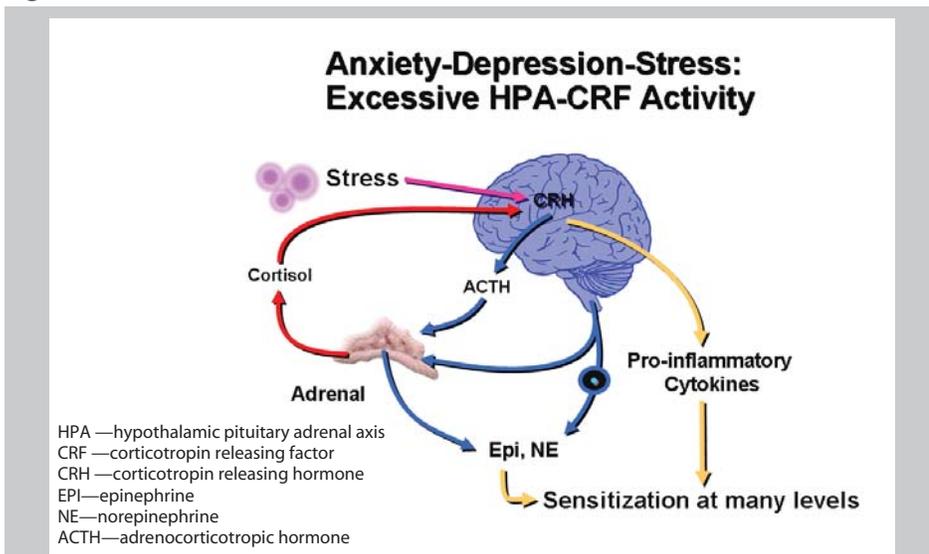
Benefits Understanding the neurobiological connection between anxiety, depression, and pro-inflammatory cytokine activity may provide insight into the importance of the anti-inflammatory effects of antidepressants in reducing distress and preventing adverse long-term health outcomes.

Persistent, uncontrolled stress is associated with the development of cardiovascular, immune, and metabolic disorders, including hypertension, atherosclerosis, type II diabetes, abdominal obesity, and other medical problems.^{2,3} Stress is operationally defined as perceived threat in combination with a perceived lack of control over the stressor.² From a clinical perspective, both anxiety disorders and depression also fulfill this operational definition of stress. Thus, in addition to being worsened by and even caused by stress, anxiety and depression are themselves stressors. Accruing evidence indicates that medical disorders known to be related to persistent stress are also associated with these psychiatric disorders.

Anxiety, depression, and stress: more alike than different?

Clinicians are keenly aware of the enhanced stress reactivity of patients with anxiety and mood disorders. The acute stress response is mediated by activation of the hypothalamic-pituitary-adrenal (HPA) axis. Hypothalamic neurons release corticotrophin-releasing factor (CRF), leading to increases in plasma cortisol and catecholamine levels. At the same time, peripherally released CRF activates the immune system, causing the release of pro-inflammatory cytokines (interleukin 1, interleukin 6, tumor necrosis factor-alpha).^{3,4} When the acute stress resolves, the stress response is shut off by cortisol acting at the glucocorticoid (GC)

Figure 1



Activation of the HPA axis results in increased cortisol production, catecholamine release, and an acute increase in pro-inflammatory cytokine release. This process is terminated by cortisol at the glucocorticoid receptor in the brain; when stress is severe or persistent, the stress system is not completely shut down, allowing for continued release of stress mediators.

a survey of comorbidity of anxiety disorders and medical illness that controlled for gender, depression, and substance abuse. Individuals with panic disorder or generalized anxiety disorder reported two to six times higher rates of cardiac disorders, hypertension, respiratory and genitourinary problems, and migraine than those without anxiety. The findings were not likely to represent over-reporting, since only 4 of 14 conditions surveyed were significantly higher than those with anxiety disorders.⁷ These findings have public health implications: could early detection and treatment of anxiety disorders and depression improve long-term health outcome? We won't know until long-term research sheds some light on this important question.

Cytokines and the sick syndrome

A dramatic demonstration of the potent brain effects of pro-inflammatory cytokines are the effects of therapeutic pro-inflammatory cytokine immune therapy in humans. Patients receiving interferon-alpha frequently experience anhedonia, anorexia, social withdrawal, fatigue, anxiety, and

depressed mood. This cytokine-induced "sick syndrome" closely resembles major depression.^{4,8-12}

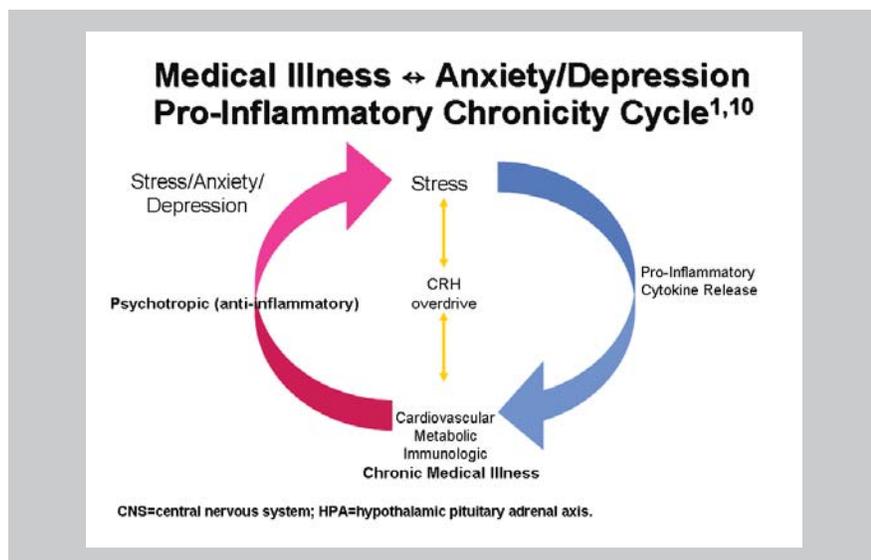
Pre-treatment with antidepressants can attenuate or prevent the appearance of these symptoms. Based on these findings, some investigators postulate that these inflammatory mediators play a role in the etiology of major depression.⁹ One proposed mechanism by which cytokines may influence affective states is by modifying HPA axis reactivity and neurotransmitter release in a fashion that resembles the stress response.⁴ Furthermore, synergy of released pro-inflammatory cytokines with psychogenic and neurogenic stressors has been demonstrated. Synergy has also been demonstrated with combined "subthreshold" doses of cytokines that alone have no effects but in combination can activate the HPA axis.³ Analogous to repeated stress, repeated release of pro-inflammatory cytokines elicits increasingly greater neural sensitization not only in the HPA axis but also in critical neuronal circuits in the brain that modulate the stress response (Figure 2).¹¹

Anti-inflammatory Effects of Anti-depressants

Antidepressants of several classes reduce cytokine production by immune cells in vitro,^{9,10} in animal models of stress-induced depression,¹¹ and in depressed patients.¹² In depressed humans, several antidepressants have also been shown to reduce levels of proinflammatory cytokines and also to increase the production of anti-inflammatory cytokines, thus tilting the ratio of anti-inflammatory to pro-inflammatory activity in a favorable direction.^{10,12}

Consistent with the stress-diathesis model of depression, cytokine synthesis and release provokes neuroendocrine and brain neurotransmitter changes that are interpreted by the brain as being stressors and contribute to the development of depression.⁴ Agents currently in the development pipeline such as CRF antagonists may be especially helpful for individuals with excessive cortisol secretion (e.g., melancholic depression, chronic anxiety, or stress).³

Figure 2



Antidepressants can attenuate the effects of pro-inflammatory cytokines via reduction in synthesis, altered ratios of pro- and anti-inflammatory cytokine production, by corrective effects on the stress axis, or possibly all of the above.

References

- Kiecolt-Glaser JK, McGuire L, Robles TF, Glaser R. *Psychosom Med.* 2002; 64(1):15-28.
- McKewen BS. *Biol Psychiatry.* 2003 54(3):200-207.
- Charmandari E, Tsigos C, Chrousos G. *Annu Rev Physiol* 2005;67:259-84
- Anisman H, Merali Z. *Ann Med.* 2003; 35(5):2-11.
- Pariante CM, Makoff A, Lovestone S, Feroli S, Heyden A, Miller AH, Kerwin RW. *Br J Pharmacol.* 2001. 134(6):1335-43.
- McKinley E. *PsychEd Up* 2005;4:5.
- Fernandez-Real JM, Ricart W. *Endocrine Reviews* 2003; 24 (3):278-301.
- Harter MC, Conway P, Merikangas K. *Eur Arch Psychiatry Clin Neurosci.* 2003;253(6):313-320.
- Raison CL, Miller AH. *Am J Psychiatry.* 2003;160(9):1654-65.
- Kenis G, Maes M. *Int J Neuropsychopharmacol* 2002. 5(4): 401-12.
- Kubera M, Lin AH, Kenis G, Bosmans E, van Bockstaele D, Maes M. *J Clin Psychopharmacol* 2001;21(2):199-206.
- Hayley S, Anisman H. *Curr Pharm Des* 2005.11(8): 947-62.
- Maes M. *Hum Psychopharmacol* 2001.16(1):95-103.

New research is now beginning to shed light on how we can literally worry ourselves sick.

While it is unlikely that pro-inflammatory and anti-inflammatory cytokines will tell the whole story, emerging evidence increasingly suggests that anxiety and depression, like stress, may promote pro-inflammatory states with health effects occurring well beyond the brain. The medical literature has described patients with syndromes that include complaints of emotional distress, muscle pain, fatigue, and gastrointestinal discomfort for centuries. These patients have received often derogatory labels including hysteria, neurasthenia, and hypochondriasis. New research is now beginning to shed light on how we can literally worry ourselves sick.

The bottom line—The concept of mind-body separation is no longer a tenable model. Anxiety and depression, like stress, can have wide-ranging physiological effects that are potentially harmful to your health. Antidepressants can therefore benefit the whole body as well as the brain.⁶ By normalizing GC receptor-HPA axis function, antidepressants exert "anti-inflammatory" effects by reducing the persistent release of humoral mediators of inflammatory activity which can contribute to long-term adverse health outcomes. Understanding the physiology of neuro-endocrine-immune function can help guide the developments of better treatments in the future. ♣