Worried Sick: Antidepressants, Stress, and Inflammation

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Antidepressants are useful for treating many disorders beyond clinical depression. In this month's column, the concept that the main therapeutic effects of antidepressants are due to their stress-buffering properties will be discussed. Anxiety, depression, and stress are inextricably linked. *Stress* is operationally defined as perceived threat in combination with an inability to control the stress.[1] Both anxiety disorders and depression meet these criteria as stressors. As would be expected, they exert negative effects when they co-occur with other psychiatric and medical disorders.[2–4] Over the longer term, anxiety and depression promote the risk for the development of certain inflammatory medical conditions associated with stress, 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.[3–7] Stress-related release of pro-inflammatory cytokines is thought to be an important mediator of the long-term adverse health effects of stress.

The neuropeptide corticotropin-releasing factor (CRF) plays a central role in stress, anxiety, and mood disorders.[1–4,6,8] The acute stress response is initiated by CRF activation of the hypothalamic-pituitary-adrenal (HPA) axis, followed by increased levels of circulating cortisol, catecholamines, pro-inflammatory cytokines, and others. Cortisol brakes and shuts off CRF release via feedback inhibition at brain glucocorticoid (GC) receptors.[6] If stress (including anxiety or depression) is sufficiently severe or persistent, the stress response may not be completely terminated.[1,4,6,8,9] Unrestrained CRF hyperactivity and continued release of pro-inflammatory cytokines and other stress mediators can result in sustained excessive inflammatory activity.[1,4,6]

Circulating pro-inflammatory cytokines stimulate the HPA axis and promote further CRF release.[8] Without HPA axis control by cortisol feedback, repeated release of pro-inflammatory cytokines elicits increasingly greater sensitization effects in the HPA axis and in critical neuronal circuits, which modulate the stress response and the emotional response to stress. To make matters worse, pro-inflammatory cytokines disrupt GC receptor function, further reducing the capacity of cortisol to provide the feedback inhibition required to shut off CRF release.[10] In humans, even the seemingly minor stress of worrying or experiencing other negative emotions (i.e., anxiety, depression) is associated with increased levels of interleukin 6 and other pro-inflammatory cytokines.[7]

Several lines of evidence link pro-inflammatory cytokines to mood and anxiety disorders. Therapeutic administration of interferon alfa immunotherapy induces depressed mood, anhedonia, anorexia, social withdrawal, fatigue, and anxiety symptoms referred to as the "sick syndrome" in the majority of recipients. Pretreatment with selective serotonin reuptake inhibitor antidepressants can reduce the emergence of these cytokine-induced symptoms by about one half.[8] These findings have led to speculation that these inflammatory mediators play a role in the etiology of major depression.[6,8,10,11]

Antidepressants may theoretically exert their stress-buffering effects via several related mechanisms. Preclinical evidence has shown that several different classes of antidepressants reduce the synthesis of CRF in key brain areas, and that they normalize post-synaptic responsivity to applied CRF in previously sensitized neurons,[9] thus attenuating previously amplified CRF effects. Evidence is also accruing that the therapeutic effects of antidepressants may be at least in part due to their anti-inflammatory effects. In depressed humans, several classes of antidepressants have been shown to reduce pre-treatment levels of pro-inflammatory cytokines and/or to increase the production of anti-inflammatory cytokines, tilting the ratio of anti-inflammatory to pro-inflammatory activity in a favorable direction.[12–16]

The evidence that anti-inflammatory actions are responsible for beneficial effects of antidepressants is not entirely consistent. Others have found no differences in pro-inflammatory cytokine levels between depressed and nondepressed patients,[17] and one recent report found that antidepressant treatment was accompanied by reductions in the levels of the inflammatory marker C-reactive protein but that it was not correlated with clinical response to treatment for major depression.[18] Another potential mechanism by which antidepressants exert stress-buffering effects includes increased transcription and synthesis of intracellular neurotrophins such as brain-derived neurotrophic factor (BDNF) and others. These enhance neuronal resilience and promote synaptic connection formation.[12,19] Antidepressant treatment has also been shown to normalize disrupted GC receptor functioning,[6,20] which theoretically allows the re-establishment of HPA axis homeostasis.

Clearly, more research is needed in order to clarify which actions of antidepressants are essential for their therapeutic effects. As more information accrues, more robust and targeted therapies may be developed to help the many who suffer from stress-related disorders.

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