ARE CHRONIC INFLAMMATION AND ITS METABOLIC COUNTERPART, INSULIN RESISTANCE, THE COMMON DENOMINATORS FOR ALL CHRONIC BEHAVIORAL AND NEURODEGENERATIVE DISORDERS?  
– A REVIEW OF THE EVIDENCE 
– PART IV

DEPRESSION – IS IT TRULY AN INFLAMMATORY ILLNESS?

INTRODUCTION

Of all the behavioral and neurodegenerative disorders considered so far in this series, there is no question that, from a clinical standpoint, the one that seems to be most prevalent and, judging from the use of SSRIs in this country, generating the most concern, is depression. Of course, depression as a clinical concern among both allopathic and alternative practitioners is nothing new. Allopaths, as noted above, have been dealing with depression with highly variable levels of success for years, mainly with SSRIs. Unfortunately, studies continue to be published, one as recently as the time of the writing of this newsletter (June 8, 2016), increasingly questioning the efficacy of SSRIs. In “Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis” by Cipriani et al (1) the authors state:

“...When considering the risk-benefit profile of antidepressants in the acute treatment of major depressive disorder, these drugs do not seem to offer a clear advantage for children and adolescents.”

Of course, as I have been pointing out throughout this series, this news about lack of efficacy of SSRIs has been known for years by those practitioners outside of the allopathic community, who have been involved in the treatment of depression. Therefore, practitioners outside of the allopathic community, which would include not only alternative medicine practitioners but psychologists and counselors, etc. have tended to approach depression as an issue of psychological stress involving adverse life experiences, either past or present, that makes people unhappy and “depressed.” Based on this assumption, treatment has generally revolved around counseling that helps patients regard life experiences differently and/or alternative medicine therapies that address the principal hormones and neurotransmitters that are involved in feeling bad about life experiences, cortisol and the catecholamines. Does the large body of literature that suggests depression is an inflammatory illness make these traditional psychological, stress-related approaches obsolete? Given the success attained by many psychologists, counselors, and alternative medicine practitioners who use modalities that optimize stress hormones, many would answer “NO”. However, I would assume that, like those practitioners employing SSRIs, practitioners employing counseling and stress hormone optimizing modalities have experienced enough patients who did not respond as expected to hopefully allow room for the idea that expanding diagnostic and treatment horizons to include a somewhat radical concept like inflammation would be both appropriate and most welcome. Therefore, the intent of this series on inflammation and neurologic dysfunction, contrary to how it may appear at first glance, is not to commit counseling, alternative treatment modalities that address stress hormones and neurotransmitters, and even SSRIs to the trash heap as outdated and outmoded. Rather the intent is to add to these existing treatment options, filling in the spaces, so to speak, where these modalities have not performed as desired.

ARE THE WORLDS OF NEUROINFLAMMATION, NEUROENDOCRINOLOGY, AND NEUROTRANSMITTERS SEPARATE ENTITIES?

As I mentioned, most practitioners tend to regard depression as a psychological stress-related issue that is best addressed via counseling and/or the measurement and optimization of neurotransmitters
such as serotonin and stress hormones such as cortisol and catecholamines. Therefore, I would suspect there might be a natural reaction to not get involved with neuroimmunology with depressed patients because it is totally foreign to these customary diagnostic and treatment modalities. Interestingly, the paper “Neuroimmune and neuroendocrine abnormalities in depression: two sides of the same coin” by Horowitz and Zunzain (2) suggests that this reaction may not be based on reality. In fact, the authors suggest that addressing neuroinflammation in depressed patients will be a logical extrapolation of what is already being done with counseling and pharmaceutical and nutraceutical modulation of stress hormones and neurotransmitters. In hopes that an understanding of this relationship will make it easier for you to start incorporating efforts to reduce inflammation along with your usual treatment efforts with depressed patients, I am now going to review this paper in detail.

In the first paragraph of the paper the authors waste no time in demonstrating how neuroendocrinology and neuroimmunity are related in depressed patients:

“Increasing evidence suggests that chronic psychological stress induces biological abnormalities, particularly in endocrine and immune systems, which manifest as increased likelihood of illness, including depression. A dysfunctional endocrine system, primarily the hypothalamic-pituitary-adrenal (HPA) axis, and a dysfunctional immune system, primarily the proinflammatory cytokine network, are frequently observed in chronic stress, which itself has strong associations with depression.”

The glucocorticoid theory of depression – in depth

Next, Horowitz and Zunszain (2) provide a detailed exploration of the stress hormone hypothesis of depression:

“The most extensively studied biological response to stress in humans is the activation of the HPA axis. Cortisol – the systemically active, human glucocorticoid – is released by this axis in response to stress and allows for a number of adaptive responses in the context of threat, both physiological and psychological. Chronic stress can lead to abnormalities of both

steady-state and dynamic responses of the HPA axis. Such abnormalities are also among the most common findings in depression and include increased pituitary and adrenal gland volume, increased levels of cortisol (in saliva, cerebrospinal fluid (CSF), blood, and urine), which are found in about 50% of depressed patients and up to 80% of severely depressed patients, and blunted cortisol stress reactivity and impaired stress recovery, especially in more severely depressed patients.”

Of course, I would suspect most readers of this newsletter are familiar with the information in the above quote. However, the following quote presents additional information on the cortisol/stress/depression story that may be less well known but much more important in terms of understanding why stress hormones and neuroinflammation are two sides of the same coin:

“Functional impairment of the glucocorticoid receptor (GR) is also common in depression. The GR, extensively distributed throughout the hippocampus, is responsible for the feedback mechanisms that regulate the HPA axis through transduction of intracellular signaling secondary to glucocorticoid ligation. The most widely identified aspect of GR dysfunction in depression is glucocorticoid resistance, involving impaired HPA axis feedback inhibition.”

What does this mean in simple terms? With long term stress, cortisol production cannot readily be “turned off” so to speak, due to glucocorticoid resistance of negative feedback receptors in the hippocampus, leading to depression. Research involving this disturbance in negative feedback has led to the glucocorticoid theory of depression, as noted by Horowitz and Zunszain (2):

“These findings have led to the formulation of the glucocorticoid theory of depression, whereby chronic stress causes abnormally high activity of the HPA axis in susceptible individuals, resulting in the production of excess cortisol, which, in turn, contributes to the neuropathology observed in depression.”

Before continuing, I do want to mention in passing a subject that I will explore in much more detail
later, the nutraceutical which has been demonstrated to assist in the optimization of glucocorticoid receptor activity in the hippocampus, phosphatidylserine.

The inflammatory theory of depression

Horowitz and Zunszain (2) next provide their explanation of the inflammatory theory of depression:

“More recently, there has been increasing recognition of the role of the innate immune system in depression.”

The authors continue:

“Like cortisol, proinflammatory cytokines can produce many of the neurological changes thought to be characteristic of depression in animal and cellular models, including decreased neurogenesis, regional brain abnormalities, changes in the monoamine system, and neurodegeneration. In addition, converging lines of evidence – the overlap between cytokine-induced sickness behavior and depression, the increased incidence of depression in medically ill patients, the induction of depression in humans and animals by stimulating cytokine production, and preliminary evidence that reducing levels of cytokines has antidepressant effects – has led to the formulation of the cytokine theory of depression. This theory and the glucocorticoid theory of depression have typically been considered in isolation until recently.”

The glucocorticoid and cytokine theories of depression: What do they share in common?

The key to understanding why the stress/glucocorticoid and inflammatory theories of depression are two sides of the same coin as opposed to separate, isolated entities as they have been traditionally regarded can be distilled down to the one word they share in common – cortisol. As was stated above, cortisol plays a major role in stress-induced depression. However, as we all know, cortisol also plays a vital role in regulating inflammation. Could this commonality create a reality where the neuroendocrine and neuroimmune systems are, in fact, intimately interlinked instead of completely separate as is typically assumed?

Consider the following quote from Horowitz and Zunszain (2):

“The innate immune system affects the HPA axis at many levels: proinflammatory cytokines induce the release of corticotrophin releasing hormone (CRH) and adrenocorticotrophin (ACTH), and induce GR resistance by direct interaction with the GR through various mechanisms, including disruption of GR translocation, GR-DNA binding through protein-protein interactions, and alterations in GR phosphorylation status.”

As demonstrated in the above quote, chronic stress-induced elevation in cortisol is not the only entity that can create glucocorticoid resistance. Chronic inflammation can do the same. This is the essence of why the stress/glucocorticoid/neurotransmitter theories of depression and inflammatory theories of depression are inextricably interlinked – both involve the creation of glucocorticoid resistance.

Of course, I would suspect that many of you may be questioning the validity of the above hypothesis stating that elevations in cortisol and excess neuroinflammation cannot co-exist because cortisol is anti-inflammatory. In the next paragraph Horowitz and Zunszain (2) address this apparent contradiction:

“Given the robust inhibitory actions of cortisol on the innate immune system, two theories have been proposed to account for the apparently paradoxical overactivity of both the innate immune system (as shown by increased levels of proinflammatory cytokines) and the HPA axis (as shown by hypercortisolemia) in depressed patients. The first highlights the role played by glucocorticoid resistance, and the second proposes hitherto underappreciated proinflammatory properties of glucocorticoids…”

Glucocorticoid resistance

For as long as we as clinical nutritionists have been routinely measuring salivary cortisol we have been wondering why we see elevated cortisol so often in highly inflamed patients such as those with rheumatoid arthritis, etc. Finally, a large body of research has provided one simple yet profound answer. Similar to insulin resistance where, very often, insulin does not function properly even
though the patient might be in a state of hyperinsulinemia, glucocorticoid resistance, where cortisol does not work properly even in the face of elevated levels, is quite common in depressed patients and other chronically ailing individuals experiencing chronic inflammation. Horowitz and Zunszain (2) state:

“The glucocorticoid resistance hypothesis proposes that, despite the commonly observed increase in cortisol levels, there is less intracellular glucocorticoid signaling in depressed individuals, favoring increased levels of innate immune signaling.”

From an evolutionary standpoint, why would the body do this? The authors note:

“The theory is consistent with an evolutionary narrative that holds that organisms continually exposed to stress require enhanced immunity to deal with likely damaging stressors. Supporting this account, animals exposed to a dominant cage mate develop glucocorticoid resistance in proportion to the number of wounds received.”

Furthermore, as suggested above, glucocorticoid resistance is not limited to patients suffering from depression:

“…a number of disorders characterized by excessive inflammatory responses, including rheumatoid arthritis, asthma, and inflammatory bowel disease, in addition to depression, have been associated with resistance to the inhibitory effects of glucocorticoids.”

In fact, from a general standpoint, in chronically stressed individuals, there is a generalized shift away from glucocorticoid activity and towards immune activity:

“There is evidence that in populations that are chronically stressed (with relevance to depression), the homeostatic balance is tipped in favor of immune signaling, away from glucocorticoid signaling.”

In the next quote, Horowitz and Zunszain (2) provide more detail on the relationship between increased innate immune activity and glucocorticoid resistance:

“The link between stress and enhanced innate immunity, mediated by glucocorticoid resistance, has been extended to dynamic responses of innate immunity. In comparison to nonstressed controls, stressed individuals have shown increased glucocorticoid resistance, an increased likelihood to develop a cold after rhinovirus seeding, and increased levels of proinflammatory cytokines (IL-1β, tumor necrosis factor (TNF)-α, and IL-6) in nasal secretions. A strong correlation between glucocorticoid resistance and levels of proinflammatory cytokines was also detected. This work provides evidence that increased inflammatory responses in glucocorticoid-resistant individuals, secondary to stress exposure, may underlie the increased susceptibility to illness of stressed individuals, and may be pertinent to depressed patients.”

In addition:

“The glucocorticoid resistance hypothesis predicts that in depressed individuals, increased levels of proinflammatory cytokines and high levels of cortisol will be present only in the context of glucocorticoid resistance.”

Can glucocorticoid resistance be present even when cortisol is not elevated? The authors point out the following based on a number of population studies on depressed patients:

“In these depressed groups, increased levels of proinflammatory cytokines and an increased incidence of glucocorticoid resistance were more common findings than increased levels of cortisol. It was particularly interesting that no studies reported increased levels of cortisol and proinflammatory cytokines without also finding evidence of glucocorticoid resistance.”

Next, consider the following:

“Indeed, glucocorticoid resistance and increased levels of proinflammatory cytokines largely co-occurred; glucocorticoid resistance was found in 85% of the studies that reported increased levels of inflammation.”

With the above in mind Horowitz and Zunszain (2) make it clear that, in depressed patients the amount
of glucocorticoid signaling is much more important than isolated levels of cortisol.

As I hope you can see, the fact that glucocorticoid resistance is virtually universal in depressed patients, and quite possibly in all chronically ill patients, has profound clinical implications in terms of understanding that the psychological stress and inflammatory theories of depression are not isolated and contradictory (as many have surmised) but intimately interlinked. All these years, we have thought that knowing cortisol levels was central to understanding why stressed, depressed people are stressed and depressed. In fact, cortisol levels are a significant but comparatively small part of the story. To truly understand the story of these patients we need to fully appreciate that, no matter what the cortisol levels, glucocorticoid resistance and its intimate counterpart, chronic inflammation, are two of the most important metabolic instigators of chronic depression. In turn, interventions that emphasize optimization of both stress physiology (counseling, meditation, yoga, adaptogenic herbs, etc.) and inflammation will most likely yield the best and most predictable clinical results.

**Glucocorticoids as proinflammatory agents?**

I realize that this suggestion goes against everything we have learned about cortisol for decades. However, an ever increasing body of research suggests that cortisol, contrary to what we thought was unassailable fact, is only anti-inflammatory under certain circumstances. In other circumstances, as I will point out, it can be pro-inflammatory and, therefore, part of the depression/inflammation story in addition to glucocorticoid resistance. Horowitz and Zunszain (2) elaborate:

“Another proposed hypothesis to explain the coexistence of high levels of inflammation and glucocorticoids in depressed individuals suggests that glucocorticoids are not uniformly anti-inflammatory, as has been previously supposed, but can be both pro- and anti-inflammatory depending on the circumstances, and, in particular, proinflammatory under specific conditions. The timing of glucocorticoid actions to an inflammatory insult is thought to be critical: actions that coincide or follow are thought to be anti-inflammatory, while those that precede are likely to be proinflammatory. This is consistent with an evolutionary narrative that outlines the utility of immunosuppressant effects during the period of an acute threat, accompanied by increased levels of glucocorticoids, given the energetic demands of fight or flight response. This is followed by a period in which recovery from damage sustained is likely to be prioritized, accompanied by a normalization of glucocorticoid levels and an enhancement of immune function.”

With the above in mind, the authors come to an extremely important conclusion:

“In this view, an incident of stress and the attendant rise in glucocorticoid hormones is seen as a neuroendocrine warning signal, priming central and peripheral cells for potential danger.”

With this quote in mind, the reality of the initial rise in cortisol during stress is that the rise in cortisol is only intended to suppress inflammation in the short term. In fact, this initial rise in cortisol early on during stress is also intended to actually facilitate inflammation in the long term.

Knowing the above, consider the inflammatory response in the central nervous system. As you may recall, the central nervous system inflammatory response is primarily mediated by microglial cells. As pointed out in the quote that follows, short term stress induced cortisol or short term glucocorticoid administration will inhibit microglial inflammatory activity:

“Microglia respond strongly to inflammatory stimuli by producing proinflammatory cytokines and other inflammatory mediators, responses that are inhibited by glucocorticoid administration or stress exposure following inflammatory stimulation.”

However, a chronic scenario actually stimulates microglial activity:

“Chronic stress has been shown to increase the density of microglia in the hippocampus, while priming these cells into their active, more proinflammatory state. Glucocorticoids have a similar effect.”
What are the mechanisms of the proinflammatory effect of glucocorticoids? Horowitz and Zunszain (2) state:

“Several components of immunological pathways are upregulated following acute or chronic stress, or glucocorticoid treatment, from cell-surface receptors to intracellular signaling molecules, which may underlie the proinflammatory effects of glucocorticoids. Glucocorticoids have been shown to induce or enhance the expression of several cytokine receptors in peripheral immune cells, including those for TNF-α, IL-1, IL-2, IL-6, IFN-gamma, and GM-CSF…”

The authors continue:

“A wide variety of cell types are responsive to glucocorticoid-induced stimulation of cytokine receptor expression, including epithelial cells, hepatic cell lines, lymphocytes, monocytes, and neutrophils.”

Some final thoughts from the Horowitz and Zunszain paper

Horowitz and Zunszain (2) conclude their paper by first looking at both reasons why glucocorticoids may be related to increased inflammation in depressed patients – either glucocorticoid resistance or direct stimulation:

“Whether increased levels of proinflammatory cytokines in depression are explained by the proinflammatory actions of glucocorticoids or by a reduction in glucocorticoid signaling secondary to receptor resistance has important implications for understanding the pathogenesis and treatment of depression. In the former explanation, increased levels of glucocorticoids are conceptualized as a driver of inflammation, suggesting that overactivity of the HPA axis may be of central importance. By contrast, the latter hypothesis suggests that even in the presence of increased levels of cortisol, reduced glucocorticoid signaling is the essential issue.”

Before continuing, please note again the last sentence in the above quote. For, it cannot be emphasized enough, given how much importance we have placed on salivary cortisol testing in chronically ill, chronically stressed patients for close to 20 years now. Because of virtually omnipresent receptor site resistance, high or low levels of salivary cortisol can be quite misleading in terms of providing an understanding of the patient and coming up with effective treatment. In contrast, as suggested in the following quote, to truly understand and effectively treat these patients we must realize that we must examine a much bigger picture that includes but is not limited to cortisol:

“Measurement of cortisol levels in isolation in stress and depression may be less pertinent than a broader focus on wider measured neuroendocrine and neuroimmune processes.”

What might this “broader focus” look like clinically? One possibility would be to, in addition to salivary cortisol testing, look at several analytes on organic acids testing plus direct measurements of inflammation seen on blood chemistry testing such as C-reactive protein, white blood cell count, AST, ALT, and sedimentation rate. Indirect measurements of inflammation on blood chemistry testing would be indicators of insulin resistance such as elevations in fasting glucose, glycosylated hemoglobin, and total and LDL cholesterol. Once the presence of chronic inflammation is established, we will now realize that efforts to treat high or low cortisol without concurrently making efforts to optimize inflammation could very well be an exercise in frustration in terms of predictable patient responses from patient to patient.

In the next installment of this series I will continue my exploration of research that considers the idea that chronic inflammation is a foundational instigator of many if not most cases of depression.

REFERENCES