

## REVIEW

# Post-traumatic stress disorder: revisiting adrenergics, glucocorticoids, immune system effects and homeostasis.

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This review focuses on post-traumatic stress disorder (PTSD). Several sequelae of PTSD are partially attributed to glucocorticoid-induced neuronal loss in the hippocampus and amygdala. Glucocorticoids and adrenergic agents cause both immediate and late sequelae and are considered from the perspective of their actions on the expression of cytokines as well as some of their physiological and psychological effects. A shift in immune system balance from Th1 to Th2 dominance is thought to result from the actions of both molecular groups. The secretion of glucocorticoids and adrenergic agents is commonly induced by trauma or stress, and synergy between these two parallel but separate pathways can produce long- and short-term sequelae in individuals with PTSD. Potential therapies are suggested, and older therapies that involve the early effects of adrenergics or glucocorticoids are reviewed for their control of acute symptoms. These therapies may also be useful for acute flashback therapy. Timely and more precise glucocorticoid and adrenergic control is recommended for maintaining these molecular groups within acceptable homeostatic limits and thus managing immune and brain sequelae. Psychotherapy should supplement the above therapeutic measures; however, psychotherapy is not the focus of this paper. Instead, this review focuses on the probable molecular basis of PTSD. Integrating historical findings regarding glucocorticoids and adrenergic agents into current research and clinical applications returns the focus to potentially life-changing treatments. Autologous adoptive immune therapy may also offer utility. This paper reports clinical and translational research that connects and challenges separate fields of study, current and classical, in an attempt to better understand and ameliorate the effects of PTSD.

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Post-traumatic stress disorder (PTSD) represents a challenge for both those who experience it and for health-care providers. We define PTSD as a condition that may arise immediately or many years after exposure to a serious traumatic event or injury. PTSD can be characterized by revisiting the initial trauma and may be accompanied by the following: anxiety, insomnia, nightmares, memory loss, behavioral changes, hyper-vigilance and hyper-arousal, crowd or social avoidance, cognitive changes or losses, increased susceptibility to infections, immune suppression, autoimmune diseases, depression and, potentially, violent acts. The occurrence of PTSD is not predictable, and it may not present with the same constellation of symptoms in each afflicted individual. It is difficult to discern whether a patient's symptoms are static, if they will return at all, or whether the symptoms will return more severely or as simply a temporary response to the revisitation of the original moment of trauma. This state of affairs complicates the prediction of symptoms and data analysis. However, PTSD can begin to be explained and ameliorated once the relationships among the various factors and relevant systems are understood.

Many studies only provide snapshots of patients at one point in time and thus may or may not reflect the overall progression of the disease. They also may not describe the vexing set of symptoms that a given patient may present throughout the evolution of the disease. The presenting symptoms at a given moment in time appear to be dependent upon an interplay of psychological, physiological, biochemical and structural changes that may or may not progress at the same rate, if at all. The various study results and symptoms may provide pieces that can eventually be assembled into a mosaic of a potential set of PTSD symptoms. Psychological treatments may be developed based on these symptoms as they appear, and their integration with therapies that address the organic and biochemical origins of the disease could be synergistic.

We explore primarily the complex interactions of PTSD with three separate but interrelated factors: the immune system, the actions of adrenergic molecules and the actions of glucocorticoids. These two molecular classes interact with the immune system, the brain and various other molecular responders to produce several of the early and late sequelae of PTSD. Adrenergic agents impact both pro-

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inflammatory and glucocorticoid systems. The effects and actions of psychotropic drugs in the serotonin family and in related families, which are also partially complicit in the behavioral symptoms and sequelae of PTSD, are addressed briefly in the review of current drug therapies. The control of acute symptoms including flashbacks may be enhanced by the more timely and precise management of adrenergic and glucocorticoid secretion along with the use of serotonin inhibitors and other medications.

### CONNECTING THE DOTS: THE INFLUENCE OF ADRENERGIC AGENTS AND GLUCOCORTICOIDS ON IMMUNE SYSTEM—HOMEOSTASIS REVISITED

The hypothalamic–pituitary–adrenal (HPA) axis is mobilized during stressful and traumatic events, which causes the glucocorticoid hormone cortisol to be released as the body attempts to return to homeostasis. The sympathetic nervous system is activated to release the adrenergic hormones epinephrine and nor-epinephrine. These are the classical major stress-related hormones,<sup>1</sup> which have mechanisms that are distinct from those of glucocorticoids; however, they also modulate the immune system via cytokine secretion. Dopamine, serotonin, glutamate/gamma-aminobutyric acid, neuropeptide Y and corticotropin-releasing factor may function in the modulation of stress, but they are not included in the discussions in this paper.

Sympathetic fibers descend from the brain to the bone marrow, thymus, spleen and lymph node tissues.<sup>2,3</sup> These fibers may be transmitters of stress-related signals early in trauma response and may be potential mediators of the initial effects of adrenergic and glucocorticoid responses to trauma. They may act by binding to receptors on immune system precursor cells and immature white blood cells. The role of regulatory T cells in PTSD has not been extensively studied; thus, unwanted or unpredictable effects relevant to these cells are currently not well known.

All lymphocytes have adrenergic receptors with varying densities and sensitivities. For example, natural killer (NK/CD8<sup>+</sup>) cells express a high density of high-affinity beta adrenergic receptors, and CD4<sup>+</sup> T cells have the lowest density of adrenergic receptors.<sup>4–6</sup> The HPA axis secretes stress hormones, including cortisone, and adrenergic hormones that bind to specific receptors on white blood cells or on their precursors in the bone marrow, thymus, spleen or lymph node tissue. These attachments may have diverse regulatory, metabolic and immune effects.<sup>7,8</sup> Certain behaviors and diseases also affect the stress response and the immune system (for example, alcoholism, drug abuse, chronic malnutrition and depression). Thus, the links between the stress hormones produced by the HPA axis, the immune system and behavioral patterns are strong and complex. Individuals who suffer from PTSD exhibit an upregulation of the immune response, while those in remission exhibit a downregulation of the immune response, with decreases in the number of T cells, NK cell activity, and the expression of interferon gamma (IFN-G) and interleukin 4 (IL4).<sup>9</sup> These cytokines exert varying effects on the immune response, and their absence or decreased expression may allow other cytokines to predominate.

Acute fight or flight stressors during a traumatic event are thought to cause redistribution of immune cells into the compartments in which they can act more rapidly and efficiently.<sup>10,11</sup> This effect was shown in a series of mouse models in which T cells are selectively redistributed to the skin during acute stress. The opposite occurs during chronic stress: T cells are shunted away from the skin, which leads to a diminished response to immune challenges. Accordingly, a bi-phasic stress response model was proposed: acute stress may reflect an enhancement of the immune response, and chronic stress may

reflect a suppression of the immune response.<sup>10,11</sup> The redistribution of T cells and their migration away from the skin appears to be a useful model for the study and evaluation of the immune system response. Both acute and chronic stress can be evaluated using the migration of T cells toward and away from the skin.

Most of the cell-mediated immunity and allergic responses are because of the hormonal/chemical messengers known as cytokines, produced by T-lymphocytes in response to antigen-presenting cell (APC) stimulation. These cells may have a ‘memory’ of prior exposure to foreign proteins or pathogens, or can be naive (that is, no memory). Those T cells expressing CD4<sup>+</sup> surface markers are known as ‘T-helper’ cells, and are further subdivided into ‘Th1’ and ‘Th2’ helper cells. Type 1 helper cells produce pro-inflammatory cytokines, capable of destroying pathogens and potentially neoplasms. Type 2 helper cells have a role in allergic responses, again depending upon the type of cytokine stimulated by the APC.

The paradoxical link between the immune response and chronic stress remains to be fully explained. In particular, an explanation is needed regarding the correlation of an inadequate immune response with potential increases in infections and neoplastic diseases as well as the correlation between an ‘excessive’ immune response and allergic and autoimmune diseases.<sup>11</sup> These correlations pose a complex question with regard to Th1 to Th2 conversion. The difficulty in understanding the Th1 to Th2 conversion is partially addressed by Marshall *et al.*<sup>12</sup> Marshall proposed that chronic stress elicits the simultaneous suppression and enhancement of the immune response via alteration of the cytokine expression pattern. In the current model, CD4<sup>+</sup> Th1 subsets release Th1 cytokines; these cytokines activate the inflammatory cellular immune response, which involves IL12 and IFN-G. IFN-G is strongly suppressed by IL10, which is produced via adrenergic moieties as a result of stress. This action helps to shift the cellular immune response to a Th2 anti-inflammatory response. Marshall stipulates that this shift does not necessarily occur in absolute quantities but instead occurs proportionately. Other Th2 cytokines include IL4, IL5 and IL6. Infections and neoplasms may occur when Th2 cytokines are allowed to predominate. This shift occurs via the interplay of stress hormones from the HPA activation of corticosteroids and the activation of adrenergics by the sympathetic nervous system. The effect of adrenergics on monocytes and the ensuing secretion and activity of IL10 is supported; IL10 has been implicated as a strong suppressor of Th1 helper cells and Th1 cytokines.<sup>13</sup> Hence, similar to the immune response to other types of trauma and stress, the trauma-induced shift of Th1 to Th2 in PTSD changes the balance of the cellular immune system’s response but not necessarily the overall level of activation within the immune system. Instead, this balance is shifted with the specific release of moieties that alter the immune system (as dictated by the challenges presented to the APCs). Th2 cytokines are not necessarily increased absolutely (such as during activated cellular or humoral immunity); they are also not necessarily increased to the extent to which they exacerbate autoimmune disease. The Th2 cytokines, however, may promote infections and other ‘immunologically unrecognized’ illnesses. This broader shift model of cytokines allows for the reconciliation of stress-related immune changes (as dictated by the changing pattern of APCs) and of patterns of stress-related disease states that include changes associated with post-traumatic stress.

The immunosuppression associated with chronic stress is also thought to be related to increased and prolonged stressors. Glucocorticoid production is decreased in chronic trauma and PTSD.<sup>14</sup> This reaction of the immune system is observed as its efficacy decreases because of senescence and the chronic downregulation of cortisol

receptor sites. The possible downregulation of cortisol receptors may also reduce the capacity of lymphocytes to respond to anti-inflammatory signals and allow other cytokine-mediated processes to dominate.<sup>15</sup>

It is unclear whether recurrent revisits to the original trauma by patients with PTSD have an equivalent effect on both the immune system and on the loss of neuronal/brain tissue. Individuals who currently suffer from PTSD demonstrate upregulated immune responses,<sup>9</sup> but we question whether a flashback/revisit is equivalent to the original trauma in terms of the immunological and physiological response. Are multiple or frequent flashbacks (however small) additive or cumulative, and do they produce the same result as the original trauma that caused the PTSD? Continuous spikes of glucocorticoids and adrenergics from flashbacks could suppress the activities of Th1 cells and cellular immune responses via the inhibition of IFN- $\gamma$  synthesis, the downregulation of cortisol receptors or the inhibition of the Th1-polarizing cytokines IL2, IL12 and tumor necrosis factor alpha; these polarizing cytokines are produced by the actions of APCs on CD4<sup>+</sup> lymphocytes.

McAuley *et al.*<sup>16</sup> described hippocampal changes in patients with Alzheimer's disease and stated that acute increases in plasma cortisol are associated with transient hippocampal inhibition and retrograde amnesia and that the chronic elevation of cortisol is associated with hippocampal atrophy. The authors state that the hippocampus is a 'core pathological substrate for Alzheimer's Disease and is essential for declarative memory synthesis' and that 'aging induced a 12% decrease in hippocampal activity, [which] increased to 30% by acute and to 40% by chronic elevations in cortisol.' The structural hippocampal atrophic changes that McAuley notes support Sapolsky's previous findings of the effects of corticosteroids on neural and brain tissue.<sup>17</sup> McAuley's recommendation for older patients with Alzheimer's disease is to monitor the cortisol levels for potential pharmacological intervention. Is the glucocorticoid model for Alzheimer's disease applicable to PTSD? Do patients with PTSD show the same hippocampal neuronal loss and changes that are observed during aging and in Alzheimer's disease? To further support flashback effects, adrenergics are known to promote the differentiation of Th2 cells, Th2 cytokine production and the production of IL10 by monocytes, all of which suppress the Th1 response.<sup>15,18,19</sup> Despite an early increase in NK cells in individuals with PTSD, there appears to be a decrease in the number of circulating NK cells within the 6- to 8-year period.<sup>20</sup> Vidovic's early finding of decreased NK cells at the 8-year time point was recently strengthened by Krukowski *et al.*,<sup>21</sup> who studied the effects of dexamethasone on the epigenetic mechanisms of immune suppression, and in particular, the suppression of the cytotoxic activity of NK cells. They found that NK cells demonstrated a reduced capacity to bind to tumor targets and also observed reduced production of granules with no detectable effect on granule exocytosis. Their findings also supported previous findings indicating corticosteroid-induced decreases in the levels of IL6, tumor necrosis factor alpha and IFN- $\gamma$ , as well as reduced surface expression of lymphocyte function-associated antigen 1 (LFA-1). LFA-1 is found on all T cells, B cells, macrophages and neutrophils and is involved in their recruitment to the site of infection. A conformational change that is induced in LFA-1 by T-cell receptors or by cytokine receptor signaling leads to the activation of LFA-1 and permits the proliferation of T cells. Histone acetylation, NK cytotoxicity activation and IFN- $\gamma$  production were restored via treatment with a histone deacetylase inhibitor, which demonstrates that corticosteroids dysregulate NK cytotoxic activation via an epigenetic mechanism. The effects of adrenergics combined with the downregulation of glucocorticoid receptor sites and the

effects of corticosteroids on the ensuing Th1 to Th2 shift may be among the most important factors leading to a suppressed immune response; this may subsequently lead to more infections or neoplasms in individuals with PTSD. The detrimental effects of long-term stress on immune function include not only a reduction in the activity of NK cells but also negative effects on lymphocyte populations, lymphocyte proliferation, antibody production and increases in the reactivation of latent viral infections.<sup>21</sup>

The paradox raised by the above discussion in regards to revisitation of the original trauma in cases of PTSD can be appreciated because of the accompanying potential bursts/spikes and either the return to normal or the increase in the levels of adrenergics and glucocorticoids. The complex relationship between chemical and physiological systems may produce a confusing mosaic of symptoms in patients with PTSD. Delayed wound-healing and impaired responses to vaccination are also observed. The senescence of receptor sites may also contribute to immune dysregulation in PTSD.

Some time ago (2000), Sapolsky *et al.*<sup>17</sup> proposed that the rat hippocampus loses neurons with age and that this loss correlates with functional impairments that are typical of senescence. The extensive loss of hippocampal glucocorticoid receptors and neuronal cells was observed in rats treated with prolonged exposure to corticosterone, as well as in aged rats. Autoradiographic analysis showed an infiltration of glial cells in response to neural damage. This is an important and classic study, the results of which may also support the concept of a process for the cellular repair and maintenance of the traumatized brain. A 5-year longitudinal study also demonstrated that long-term exposure to rising cortisol levels in healthy elderly human patients led to a 14% decrease in hippocampal volume that correlated with significantly impaired memory.<sup>22</sup> The loss of ~14% of the neural tissue may represent a critical mass or tipping point of loss that deserves further investigation to determine its potential integration into clinical practice.

Hippocampal atrophy has also been found in many patients with depression and in veterans with chronic PTSD.<sup>23</sup> Hippocampal neuronal atrophy may be explained in part by higher levels of glucocorticoids, as increased levels of glucocorticoids significantly inhibit glucose uptake by neurons not only in hippocampal cells<sup>24</sup> but also in most cell types. This inhibition renders the neurons and other cells susceptible to damage by free radicals and other mechanisms.<sup>25</sup> Glucose is required for sustained cell metabolism, and the shift to anaerobic metabolic pathways is usually associated with a shortened cellular lifespan.

As stated above, several similarities between PTSD and chronic stress have been demonstrated by various studies; these similarities implicate a Th1 to Th2 shift in the immune response that is stimulated by glucocorticoids and adrenergics. These two molecular groups appear to have similar effects on the immune system, albeit via different mechanisms or pathways. In addition, glucocorticoids appear to cause a loss of neuronal tissue in various parts of the brain, which may then manifest as potentially late cognitive and behavioral changes in PTSD.

## DISCUSSION

The pharmacological treatment of PTSD has been somewhat helpful, and medications continue to represent a useful adjunct to psychotherapy, particularly in treatment of the early symptoms of PTSD. Control of the amygdala is a desired end state that can be achieved through the targeting of excessive alpha-1 and beta receptor sites and the simultaneous enhancement of alpha-2 inhibition. The role of glutamate in PTSD remains poorly understood.

An excellent review of the current pharmacologic management of the early and potentially ongoing symptoms of PTSD by Viola *et al.*<sup>26</sup> described basic drug therapy that has been and continues to be useful. These legacy therapies remain among the best that are currently available.

Clonidine, an alpha-adrenergic agonist, has been used successfully to reduce sympathetic outflow from the alpha-2 receptor sites in the central nervous system, thus decreasing peripheral vascular resistance and slowing the surge of catecholamines. This inhibits impulsive and aggressive behavior.<sup>26</sup> Nightmares, insomnia, mood changes, anger/agitation, hyper-arousal, hyper-vigilance and symptoms of depression and panic have been treated with trazodone, fluoxetine, valproic acid, carbamazepine and prazosin.

The antidepressant trazodone selectively inhibits serotonin uptake and enhances behavioral and cognitive changes via 5-hydroxytryptophan, which is a serotonin precursor.<sup>26</sup> Fluoxetine (sertraline) also inhibits serotonin uptake to enhance serotonin activity and decrease the noradrenergic response. Avoidant, intrusive and explosive behaviors have also been shown to decrease with fluoxetine treatment.<sup>27,28</sup> Obsessive-compulsive behavior, hostility and disinhibition have been minimized with divalproex.<sup>29</sup> The anti-convulsant valproic acid increases the levels of gamma-aminobutyric acid, as well as sensitivity to gamma-aminobutyric acid receptors in the central nervous system/brain to decrease limbic kindling,<sup>30</sup> which is thought to manifest as hyper-arousal, flashbacks and nightmares.

This traditional pharmacologic toolkit will likely remain helpful even if newer drugs are developed in the future. Notably, serotonin-related symptoms are also accompanied by adrenergic activity, which can influence the immune response via IFN-G and IL10. Adrenergics affect both alpha and beta receptor sites.

A more recent review of pharmacologic treatments for PTSD by Searcy *et al.*<sup>31</sup> concluded that a beta blockade in addition to corticosteroids is useful as a pharmacologic adjunct in PTSD therapy. As reviewed earlier in this paper and in the supportive literature, the effects of beta blockers enhance the Th1 cellular immune response by blocking IL10 and enhancing the anti-infection effects in stroke/brain injury.<sup>32</sup> This includes the use of alpha-1 blockers. The use of glucocorticoids in patients with PTSD contradicts the robust literature that describes the detrimental effects of glucocorticoids in PTSD, as well as the immune interactions and effects on brain tissue, as discussed above. Glucocorticoids are sometimes useful in the maintenance of tissue perfusion during septic shock and are not used for prolonged periods. The effects on a patient with PTSD who experienced combat or other serious trauma are not comparable with the effects that are observed from a single sepsis or a single surgical event that was treated with a short course of glucocorticoids.<sup>33,34</sup>

Glucocorticoids, as historical 'immune-suppressing agents', have demonstrated specific actions through the inhibition of lymphocyte proliferation, cytotoxic effects, and decreases in the secretion of IL2, IL6, IL12, IFN-G and tumor necrosis factor alpha,<sup>35</sup> among others. The literature shows that the immunosuppressive effect is specific to the inflammatory cellular immune system and that a shift from Th1 to Th2 cellular humoral immunity is strongly enhanced<sup>36</sup> through the suppression of IL12, which is a major Th1 agonist. These effects are observed over both the short and the long term.

These actions correlate with the results and conclusions provided by Marshall *et al.*,<sup>12</sup> who reported that a cytokine shift but not an absolute increase in cytokines is responsible for the immune system shift and that this shift may be induced by both glucocorticoids and adrenergics.

The peripheral utilization of glucose is inhibited by a decrease in the translocation of glucose transporters, such as GLUT4, to the cell membrane.<sup>37</sup> The inhibition of GLUT4 may lead to neuronal damage in the hippocampus and amygdala, as proposed long ago (2000) by Sapolsky *et al.*<sup>17,24,25</sup> As stated previously (1985), more recent support for Sapolsky's early findings with regard to neuronal death was provided by McAuley *et al.*<sup>16</sup> McAuley's work on the brains of Alzheimer's disease patients also provides a potential explanation for the effects of glucocorticoids on the hippocampus. He states that acute increases in plasma cortisol are associated with transient hippocampal inhibition and retrograde amnesia and that chronic cortisol elevation is associated with hippocampal atrophy. Are flashbacks a result of these effects? These findings may complement other studies and hypotheses. McAuley *et al.* used a mathematical model to investigate the effects of cortisol on the hippocampus and estimated a ~12% decrease in hippocampal activity because of aging, as well as a ~30% decrease because of acute cortisol elevations over time. He posits that an acute cortisol 'overshoot' may induce cortisol receptor transcription and the inhibition of pyramidal cells (CA1 cells) in the hippocampus; CA1 cells are thought to be involved in memory, cognition and transient amnesia. One example of this type of acute event may be the 'tip of the tongue' forgetfulness that some experience in stressful situations. Elevated cortisol may induce a change in the expression of glucocorticoid receptors and thus in the inhibition of CA1 cells.<sup>16</sup>

Glucocorticoids appear to have 'u-shaped' or inverse dose-dependent effects on the firing of hippocampal neurons.<sup>38</sup> Further complex effects of corticosteroids on the central nervous system are noted by Sorrells *et al.*,<sup>39</sup> who also describe a 'horseshoe effect' but explain that it may be due to the difference between mineralocorticoid receptors and glucocorticoid receptors and their differing affinities for corticoids; these different affinities lead to a complex and counter-intuitive opposing inflammatory response. The work of Sorrells *et al.*<sup>39</sup> also supports varying effects of the timing, dosing and effects of corticoids in various parts of the brain in their discussion of how cortisol causes inflammation.

In addition to the surprising inflammatory effects of corticosteroids and the potential explanation provided by the somewhat confusing glucocorticoid and mineralocorticoid-receptor site theory, the 'u-shaped' hypothesis raises important questions. A failure to return to homeostasis at either end of the u-shaped corticosteroid effect curve can be problematic. We believe that the u-shaped effect may represent an acceptable homeostatic response. Too little or too much cortisol may be the culprit. Homeostasis is either absent, present, emerging or excessive depending on the level of glucocorticoids, adrenergics, and, potentially, other molecules.

A major question remains unanswered: are the flashbacks of patients with PTSD 'immunologically equivalent' to the secretion and action of glucocorticoids and adrenergics that occurred during the original trauma? Another pertinent concern is whether adoptive immune therapy may alleviate the problems associated with this disorder.<sup>40</sup> The effects of these acute 'bursts' in cases of PTSD may be partially explained by McAuley *et al.*<sup>16</sup> in their discussion of the effects of aging and Alzheimer's disease on the hippocampus. However, is the same model applicable to both PTSD and AD (Alzheimer's Disease)?

Homeostasis was originally described by Selye<sup>41</sup> in his seminal study on the response to stress by corticosteroids. Selye correctly described that homeostasis is maintained by the body in response to stress and helps the organism survive during 'fight or flight' stress situations. Thus, homeostasis is beneficial for survival, but it is becoming clearer that 'more' homeostasis is not necessarily better. As discussed above, it is clear that higher and prolonged levels of glucocorticoids are not

beneficial because they destroy brain tissue, which interferes with cognition and leads to other diseases. In corticosteroid therapy, dosing within a certain range is beneficial for immune suppression in order to avoid the consequences of allergic reactions on a temporary basis. However, higher doses of corticosteroids cause the opposite effects and result in other illnesses. As mentioned above, the control of cortisol levels could potentially be used to maintain homeostasis within acceptable levels.

Yehuda and LeDoux<sup>42</sup> describe PTSD as a specific phenotype that is associated with a failure to recover from the normal effects of trauma. They suggest that research should focus on the pre- and post-traumatic risk factors that explain the development of the disorder and the failure to return to physiological homeostasis. Ducrocq and Vaiva<sup>43</sup> also discussed the disruption of the homeostatic balance during various stages of therapy in traumatized individuals and in those with PTSD. We have described some of the molecular biology that is associated with the violation of the parameters of homeostatic excesses in PTSD. Other traumas will likely present the same pathways and include genetic and epigenetic mechanisms. Nevertheless, much remains to be discovered.

Proactive therapy may be offered to individuals with potential trauma, head trauma and PTSD in the form of improved helmets, resilience training and the early identification of the risks for PTSD. Resilience training is performed in the military as one method to protect the deployed soldier and his or her family members to the rigors of war and the stresses that they may face. Resilience training is typically provided for members of the military (both active and reserve) who plan to deploy, as well as for their families and supporting military civilians. Luthar<sup>44</sup> defined resilience 'as a dynamic process encompassing positive adaptation (and not merely the absence of pathology or dysfunction within the context of significant diversity).' Saltzman *et al.*<sup>45</sup> reviewed the theoretical and empirical foundations of resilience and stressed that the family-centered FOCUS (families overcoming under stress) methods developed at the schools of medicine of both UCLA and Harvard are the primary drivers of this program. Psychotherapy that is based on symptoms may include counseling, prolonged productive therapy, questionnaires or studies and high doses of various psychotropic medications with potentially dangerous side effects. These medications may be partially responsible for the higher suicide rates observed in some soldiers and others with PTSD. We must combine psychological care with psychotropic medications on a long-term basis and balance control of adrenergics and glucocorticoids and their responses to maintain acceptable homeostatic parameters. Progesterone therapy, fear extinction studies<sup>45</sup> and new protein actions and pathways may eventually be useful. Further clinical studies will explore this exciting area of novel clinical and translational science. A systems approach may also be useful.

Hyperbaric oxygen may eventually help to ameliorate the symptoms of traumatic brain injury and PTSD and to restore brain tissue that has been lost such that some level of physical and psychological functional recovery can be achieved. Adoptive immune therapy coupled with corticosteroid and catecholamine pharmacologic therapy may be an attractive option for the amelioration of immune suppression. This would also benefit specific short- and long-term sequelae that are associated with PTSD by restoring the balance between the Th1 and Th2 immune responses. This would likely calm the 'cytokine storm' or 'catecholamine rush' that is triggered by trauma. It may also modify the Th1 to Th2 shift and the cytokine effectors that are involved by restoring the balance between the two systems with healthy, naive, autologous lymphocytes.<sup>40</sup> The effects of senescence and aging of the

receptor sites may also be overcome using adoptive immune therapy with the reinfusion of both autologous and allogenic immune cells (lymphocytes).<sup>40</sup> These therapies have proven useful in both traditional and current cancer treatment models. The more closely studied and monitored interference and modification of glucocorticoids and current anti-adrenergic treatments may also provide answers to the puzzle of PTSD symptoms, including the issues posed by McAuley *et al.*<sup>16</sup> Protecting neural tissue in the amygdala and hippocampus using glucocorticoids is an obvious potential therapeutic target. Glucocorticoid mechanisms of action are exceptionally complex because they involve epigenetic effects, receptor site effects, immune and cytokine effects (both expected and unexpected), metabolic pathway/glucose effects, and dose- and time-related effects. All of these consequences culminate in neuronal loss in the hippocampus and amygdala and in the incidence of immunosuppressive diseases. The effects of glucocorticoids and adrenergics lead to the expression of symptoms of the condition that we now refer to as 'PTSD'.

It is important to repeat our initial description of PTSD in the context of relevant and supporting research: many studies provide only snapshots during the progression of this condition; these snapshots may or may not reflect the disease process or the set of symptoms that evolves in a patient over time. However, it is also possible that nothing may change and that the same pattern of symptoms may re-appear. This issue is both vexing and problematic, and the presented symptoms appear to be dependent upon the interplay between psychological, physiological, biochemical and structural changes that may or may not progress at the same rate or at all in each patient. Various studies may contribute to the understanding of these psychological, physiological, biochemical and structural changes and how each relates to PTSD symptoms. The changing relationship between stress levels, as well as responses to stress via varying levels of glucocorticoids and adrenergics and their ever-changing effects on the immune system pose a challenge to scientists attempting to define this condition. Can this homeostasis imbalance be rectified? Treatments may be designed based upon these studies as symptoms appear. These therapies are somewhat helpful, but substantial work is needed to characterize the organic and biochemical origins of the disease and translate the relevant knowledge into clinical therapy. A first step would be to thoroughly re-explore and apply classical data regarding glucocorticoids and adrenergics and to update potential antagonist therapies that have thus far been under-appreciated or ignored. Karpova's use of fluoxetine and extinction training to produce fear erasure in mice may foreshadow a future therapeutic modality for PTSD.<sup>46</sup>

The relationship between PTSD and pain warrants exploration. Pain was defined by Turk<sup>47</sup> as a 'multidimensional, complex, subjective, perceptual phenomenon'. The co-occurrence of pain and PTSD is frequent and may even be chronic. The combination of pain and PTSD should not be ignored<sup>46</sup> because it leads to more serious functional and cognitive impairments. The pain associated with trauma and PTSD may lead to chronicity of both pain and PTSD and may result in fear-based avoidance of pain behavior, as described above.<sup>46</sup> The primary goal with respect to the treatment of concurrent pain and PTSD is to minimize or decrease the avoidance behavior either chemically with medication or for a prolonged period with psychotherapy.<sup>48</sup> Both physical and psychological injuries cause pain, but one may ask whether psychological pain is also the result of a moral injury. There are few references in the literature that address moral injuries of soldiers given the toxic leadership environment and war experiences one finds in a military setting. This paper does not focus on the psychological issues that surround PTSD and 'pain' and

does not review the extensive literature addressing the most appropriate therapeutic modality. Rather, this paper focuses on the changes observed in two molecular groups (glucocorticoids and adrenergics) and their effects on the immune system and homeostasis as they relate to PTSD. This review also discusses the presentation of PTSD in an attempt to understand and treat this condition. A secondary goal is to open novel fields of study, including the evolutionary role of homeostasis in the death of neurons and brain tissue, and to consider the potential modeling of PTSD using established AD models.

## CONCLUDING REMARKS

The traumatized PTSD brain accumulates damage over time. Neurons in the hippocampus, amygdala and other parts of the brain are destroyed by glucocorticoids. Chemical imbalances and their corresponding effects (as well as the opposite effects) may occur. Adrenergics and glucocorticoids, along with serotonin and other moieties, affect immune, chemical and structural responses to produce short- and long-term effects that we recognize as sequelae of PTSD.

The immune system, the HPA axis and their associated molecules are interdependent and constantly fluctuating in a PTSD setting. Legacy pharmacotherapy remains useful for adrenergic-related PTSD sequelae, but newer drugs await discovery. Insufficient attention has been paid to anti-glucocorticoid and adrenergic containment therapies despite robust literature that demonstrates their potential negative effects in the long term but potential positive effects in the short term (homeostasis). Perhaps revisiting classical studies and therapies can be useful. Selye's<sup>49</sup> classic model may undergo further modifications.

The questions raised and the classical science that are re-introduced in this article demonstrate a need to reflect and consider the long-term integration of adrenergic and glucocorticoid therapies. The effects of these molecular groups have not been adequately studied or explored with respect to the treatment of patients during flashback therapy. The serum or homeostatic levels and effects of adrenergics and glucocorticoids need correlation with symptoms and sequelae of PTSD and flashbacks. Too many studies and 'information overload' appear to have outpaced clinical integration and the comprehensive consideration of classical studies in patient care and rational treatment for long-term sequelae. Short-term answers must be replaced with long-term solutions. Classical research should be reintegrated into current patient care. A question remains: is it best to maintain homeostatic balance by controlling the levels of glucocorticoids and adrenergics or to treat the symptoms as they arise? Perhaps both types of therapy can be integrated to provide a balanced model, but this integration presents a challenge.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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