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Novel Pharmacological Targets for Combat PTSD—Metabolism, Inflammation, The Gut Microbiome, and Mitochondrial Dysfunction

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ABSTRACT Introduction: Current pharmacological treatments of post-traumatic stress disorder (PTSD) have limited efficacy. Although the diagnosis is based on psychopathological criteria, it is frequently accompanied by somatic comorbidities and perhaps "accelerated biological aging," suggesting widespread physical concomitants. Such physiological comorbidities may affect core PTSD symptoms but are rarely the focus of therapeutic trials. Methods: To elucidate the potential involvement of metabolism, inflammation, and mitochondrial function in PTSD, we integrate findings and mechanistic models from the DOD-sponsored "Systems Biology of PTSD Study" with previous data on these topics. Results: Data implicate inter-linked dysregulations in metabolism, inflammation, mitochondrial function, and perhaps the gut microbiome in PTSD. Several inadequately tested targets of pharmacological intervention are proposed, including insulin sensitizers, lipid regulators, anti-inflammatories, and mitochondrial biogenesis modulators. Conclusions: Systemic pathologies that are intricately involved in brain functioning and behavior may not only contribute to somatic comorbidities in PTSD, but may represent novel targets for treating core psychiatric symptoms.

INTRODUCTION

The diagnosis of post-traumatic stress disorder (PTSD) is based on severe trauma exposure and symptoms in the clusters of intrusive re-experiencing, avoidance, and persistent negative alterations in cognition, mood, and arousal.[1] These criteria do not readily lend themselves to objective determination and do not take into account underlying biological abnormalities. This makes pharmacological treatment difficult, since no clear biochemical "targets" for pharmacotherapy are identified. The current standard-of-care for the pharmacotherapy of PTSD, selective serotonin reuptake inhibitors, has limited efficacy.[2]

Combat PTSD is frequently accompanied by blast trauma and mild traumatic brain injury, which can contribute to the clinical features and pathophysiology of PTSD.[3] The present article focuses on syndromic PTSD, as defined by Diagnostic and Statistical Manual (DSM) criteria[1] apart from such physical trauma. PTSD is frequently accompanied by cardiovascular disease (CVD), metabolic syndrome (MetS), diabetes mellitus type II (DMII), autoimmune diseases, early mortality, and perhaps even "accelerated biological aging," defined as biological aging outpacing chronological aging. This suggests that PTSD is a systemic, rather than solely a brain, disorder.[4,5] Such comorbidities are rarely the focus of therapeutic trials.

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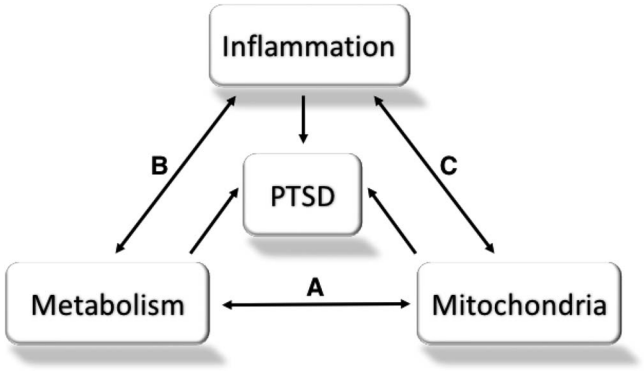

FIGURE 1. Simplified hypothetical model of interactions between mitochondrial dysfunction, metabolism, and inflammation in PTSD. (A) Inter-relationship of mitochondria and metabolic syndrome, (B) inter-relationship of metabolic syndrome and inflammation, and (C) inter-relationship of mitochondria and inflammation. For more details, see Refs. [5,35,43–46,53,56]

Accruing data suggest interlinked dysregulations in metabolism, inflammation, and mitochondrial function in PTSD (Fig. 1).[4,5] Although neuropathological abnormalities are also observed in PTSD,[6] these are beyond the scope of this article, which limits itself to these three biochemical dysregulations. Systemic biochemical pathologies may contribute both to the somatic comorbidities and the core psychiatric PTSD symptoms, since they are intricately involved in brain functioning and behavior.[5] We propose several inadequately tested targets of intervention, including insulin sensitizers, anti-inflammatories, and mitochondrial biogenesis modulators (Table 1). We integrate recently acquired data from the Department of Defense (DOD)-sponsored "Systems Biology of PTSD Study" and other recent studies[7–12] with previous clinical data and suggest novel treatment targets.

METABOLISM

PTSD is associated with MetS, obesity, DMII, and insulin resistance (IR); it has even been considered a "metabolic disorder in disguise".[13] MetS has a prevalence of 38.7% in PTSD ($p < 0.001$) and an almost double risk compared to controls.[14] Abdominal obesity, hypertension, hypertriglyceridemia, hyperglycemia, and low high density-lipoprotein cholesterol levels are observed in PTSD.[14] The rates of MetS do not differ in combat vs. non-combat PTSD, men vs. women, or individuals with comorbid major depressive disorder (MDD) vs. those without. [14]

PTSD is also associated with increased DMII, even after controlling for MDD and other psychiatric illnesses.[4,5,9] MetS and DMII are prognostic of CVD and could contribute to the increased morbidity and mortality seen in PTSD.[4] Although it is difficult to control for lifestyle factors and medications in assessing MetS and DMII in PTSD, MetS and DMII increase risk for somatic illness and add pose additional targets for intervention.

MetS and DMII may also contribute to core neuropsychiatric symptoms of PTSD. They may be associated with deleterious effects in the central nervous system, for example, heightened vulnerability to brain injury, neurodegenerative disorders, diminished cortical thickness, and impaired cognition,[5,15,16] as well as neuroinflammation, microglial activation, oxidative stress, altered serotonin metabolism, decreased brain-derived neurotrophic factor levels, decreased hippocampal long-term potentiation, altered brain-blood barrier (BBB) function and brain energetics, altered free-fatty acids and cholesterol-based constituents of brain cell membranes, and altered adipokine signaling in the brain.[17] Wolf et al. [16] found that PTSD predicted MetS, which in turn was associated with reduced cortical thickness and concluded that "PTSD confers risk for cardiometabolic pathology and neurodegeneration and raises concern that this cohort may be aging prematurely and at risk for substantial medical and cognitive decline". A polygenic risk score (PRS) associated with obesity interacts with PTSD to predict MetS, and the same PRS interacts with both PTSD and MetS to predict regional decreases in cortical volume in veterans with PTSD,[15] suggesting that brain abnormalities associated with PTSD and MetS may be compounded by genetic predispositions. The direction of causality between PTSD and MetS, if any, may be bidirectional. In a longitudinal study, PTSD severity predicted subsequent increases in MetS, but MetS did not predict subsequent PTSD.[18]

In summary, PTSD is frequently associated with MetS, DMII, and related disturbances, although not all patients with PTSD demonstrate such metabolic disturbances, highlighting the need for subcategorizing patients when considering target-based therapies. Specific pharmacological treatment strategies are discussed below.

INFLAMMATION

Elevations of inflammatory markers are among the most widely replicated biological abnormalities in PTSD.[19] It has even been suggested that PTSD is an "immunological disorder."[19] Most often elevated are interferon gamma, interleukin 6, and interleukin 1 beta; tumor necrosis factor alpha is also elevated in medication-free individuals with PTSD.[20] Increased inflammation in PTSD is observed even after controlling for age, body-mass index (BMI), smoking, early life trauma, depression, and potentially interfering mediations and somatic comorbidities.[11] Providing support for intrinsic inflammatory changes in PTSD, DNA methylation, and transcriptomic studies have identified PTSD-associated dysregulation of genes and pathways related to inflammation and immune function.[21]

The inflammatory status of individuals with PTSD may contribute to their high medical comorbidity and to their increased incidence of autoimmune disorders.[22] However, not all individuals with PTSD have elevated inflammatory indices, and in those that do, their elevations are rarely to the extent seen in primary inflammatory diseases.

Most studies assessed blood-based markers, and their relationship with neuroinflammation is not known. However, immune activation may also be found in the cerebrospinal

TABLE 1. Hypothesized Drugable Targets and Treatments in Post-Traumatic Stress Disorder

Target/Process	Drug Mechanism of Action	Examples	References
Metabolism; glucose and insulin regulation	Insulin and insulin sensitizers	Insulin (eg, intra-nasal); Metformin	36,45,53–55
	PPAR agonists/activators	Thiazolidinediones (eg, rosiglitazone/pioglitazone); PPAR/PGC-1α; pyrroloquinoline quinone (PQQ)	52,57
	Adiponectin upregulation	PPAR agonists; angiotensin receptor type I blockers; ACE inhibitors; cannabinoid receptor antagonists; thiazolidinediones; omega-3 fatty acids	64
Inflammation	Anti-inflammatories	Corticosteroids; TNF-α antagonists; aspirin; NSAID's (eg, naproxyn, ibuprofen, diclofenac); PQQ	52,60,61
Mitochondrial biogenesis	PPAR-γ coactivator (PGC)-1α coactivator	Fibrate drugs (eg, bezafibrate, fenofibrate, clofibrate); thiazolidinediones (eg, rosiglitazone, pioglitazone); PQQ	36,45,52,54,69
	AICAR (5-amino-imidazole-4-carbaxamide ribotide)	AICAR	36
	AMPK (AMP kinase activated protein kinase)	Indirect activators (eg, thiazolidinediones, quercetin, metformin, cucurmin, alpha-lipoic acid), metformin	36
	Sirtuins (SIRT 1 activator)	Quercetin; resveretrol; SRT1720	36,52,69
	Mitochondrial antioxidants	CoQ10; MitoQ; melatonin; PQQ	52,69
	Enhances ATP production	Creatine; lipoic acid; carnitine	36
	Triggers the Nrf2 antioxidant response element (ARE)	Oleanolic acid derivatives; PQQ	36,52

The table lists only the biochemical targets reviewed in this article and is updated and adapted from one previously published in Ref.[5].

fluid in PTSD.[23–25] Several mechanisms exist for peripheral immune system communication with the brain, including transport across leaky regions of the BBB such as the circumventricular organs, stimulation of vagal afferents, and trafficking of activated monocytes or other immune cells into the brain.[26] Neuroinflammation, in turn, can alter brain functioning, such as impacting serotonin, catecholamine and glutamate availability, increasing oxidative stress and the neurotoxic metabolite quinolinic acid, and accentuating amygdala response to threatening situations.[21,26]

The causes of inflammation in PTSD are unclear but may involve genetic or epigenetic determinants, a "sterile inflammation" in response to damage-associated molecular patterns, hyper-catecholaminergic and hypocortisolemic states induced by chronic stress, immune responses to various pathogens, or else autoimmune processes.[5] It is not clear whether inflammation is a vulnerability marker for PTSD or the result of trauma exposure, and these possibilities are not mutually exclusive.[27] The former hypothesis is supported by genetic studies[28,29] and by a prospective study in veterans reporting that high baseline CRP levels predicted the occurrence and severity of post-deployment PTSD, even after accounting for trauma exposure, suggesting the involvement of inflammation in risk for combat PTSD.[8]

Alterations in the gut microbiome and impairments in intestinal barrier function (IBF) may also be important in generating inflammatory responses, both peripherally and in the brain.[30,31] Psychological stress may impair IBF, allowing for translocation of bacterial components, thereby leading to inflammatory responses. These may also contribute to brain pathology and alterations in behavior via alterations of the tryptophan/kynurenine ratio, short chain fatty acid production and alterations in BBB permeability.[30] There have been no studies, to our knowledge, that specifically examined associations between the gut microbiome, impaired IBF, and inflammation in combat-related PTSD. However, a recent study in civilians with PTSD found that decreased Actinobacteria, Lentisphaerae, and Verrucomicrobia taxa play a role in maintaining IBF; these decreases were directly correlated with PTSD severity.[32] Another study in stress-exposed soldiers identified associations between reduced relative abundance of Actinobacteria and increased intestinal permeability after stress exposure.[30] The Verrucomicrobia taxon was mainly represented by a single species, *Akkermansia muciniphilia*, which has been posited to improve obesity and glucose homeostasis via restoration of IBF, suggesting that the observed gut microbiome alterations may contribute not only to inflammation but also to metabolism-related medical co-morbidities.

In summary, increased inflammatory markers are frequently reported in PTSD; these may contribute to somatic comorbidities and autoimmune diseases. Anti-inflammatory therapies could prove useful in selected individuals with

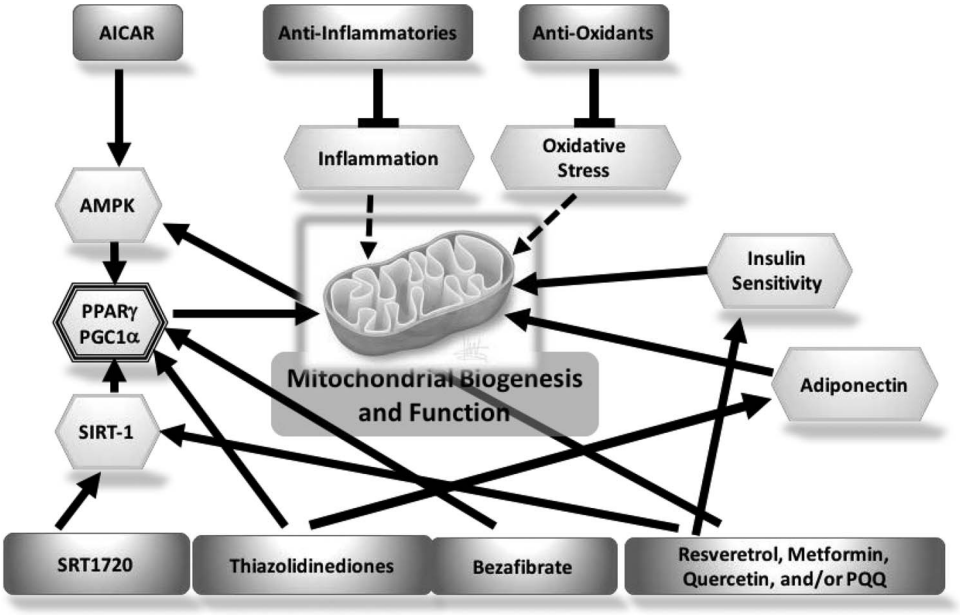

FIGURE 2. Pharmacological approaches targeting inflammation, metabolism, and mitochondrial biogenesis and functioning as potential therapeutic options for post-traumatic stress disorder. Regulators of mitochondrial biogenesis are depicted in the middle rows of the figure in hexagons, and pharmacological agents acting on them are depicted in the upper and lower rows of the figure in rectangles. *Solid arrows* indicate stimulatory effects, and *blunted bars* and *dashed arrows* indicate inhibitory ones. For more details, see Refs. [5,36,52,64–68]

evidence of increased inflammation, as discussed below. Such strategies have been investigated in individuals with major depression.[33]

MITOCHONDRIAL FUNCTION

Mitochondria play a key role in maintaining cellular homeostasis, producing energy and generating free radicals (which can be beneficial at low to moderate levels or harmful at higher levels), regulating oxidative stress, facilitating intra- and inter-cellular communication, synthesizing steroid hormones, sequestering intracellular calcium, and mediating apoptosis and detoxification.[34–36]

Dysregulated mitochondrial genes and networks, which may be related to neurological dysfunction, psychiatric disorders, stress responses, and endocrine and neuronal signaling, have been identified in postmortem human brain samples from subjects with PTSD.[37–40] The DOD "Systems Biology of PTSD" study also identified genes associated with mitochondrial function that were differentially methylated in PTSD versus trauma-exposed control subjects.[41] Metabolomic analysis showed that PTSD subjects had increased plasma levels of glucose, pyruvate, and lactate along with reduced plasma levels of citrate (suggesting possible alterations in the tricarboxylic acid cycle), and increased plasma levels of acylcarnitines (suggesting reduced mitochondrial glycolytic and fatty-acid beta-oxidation activities).[7] PTSD subjects also had reduced concentrations of several essential fatty acids and omega 3-polyunsaturated fatty acids (PUFAs).[7] Omega-3 PUFAs have anti-inflammatory and insulin-sensitizing effects mediated through their binding to GPR120 receptors.[42] Hence, reduced concentrations of omega-3 PUFAs may lead to insulin resistance and inflammation.[43–46] These metabolomic findings require replication in additional samples and establishing more direct correlations. Mitochondrial DNA copy number may also be reduced in leukocytes of PTSD subjects, further suggesting altered energy metabolism.[10] Related mitochondrial findings have also been demonstrated in brains in animal models of PTSD.[5,47–49]

Direct studies of mitochondrial function in PTSD have not yet been conducted. Longitudinal studies will be needed to determine whether mitochondrial dysregulation precedes or follows PTSD onset and if a causal relationship exists. To the extent mitochondrial dysfunction contributes to PTSD, pharmacological trials of mitochondrial enhancers, as described below, could prove beneficial.

NOVEL PHARMACOLOGICAL APPROACHES

Inflammation, metabolism, and mitochondrial functioning may be involved in medical comorbidities associated with PTSD. Targeting these may benefit core PTSD symptoms in addition to the somatic comorbidities (Table 1 and Fig. 2). Although these data should prompt further investigation, none has yet been demonstrated to treat PTSD, and none is yet indicated for PTSD.

Metabolism

Available drugs for treating MetS and DMII have not yet been investigated in PTSD, although innovative studies have

been conducted using such drugs in the treatment of MDD,[50] Alzheimer's disease, and mild cognitive impairment.[51] Drugs such as thiazolidinediones and other insulin sensitizers, as well as metformin and other antidiabetic drugs and perhaps pyrroloquinoline quinone (PQQ), should be investigated for psychiatric benefits beyond their currently recognized benefits in medical disorders.[43,45,52–57] Of note, PPAR-gamma agonists also have anti-inflammatory effects, perhaps making them especially attractive candidates for investigation in PTSD.[57] A recent meta-analysis including all studies that examined the effects of established antidiabetic drugs on depressive symptoms (in non-PTSD populations) found that pioglitazone improved depression with a large effect size.[58] These findings support studying such drugs in PTSD, although it is not known whether baseline metabolic dysregulation is required for beneficial responses.

Inflammation

Anti-inflammatory agents (eg, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, and others), which could conceivably help PTSD,[59,60] have not, to our knowledge, been investigated in PTSD in randomized clinical trials (RCTs). This is despite the fact that anti-inflammatory treatment is associated with antidepressant effects in depressed individuals who have elevated pretreatment inflammatory markers,[33] and animal studies show that ibuprofen reduced cytokines in tandem with reduced anxiety behaviors.[59] Hydrocortisone, a potent anti-inflammatory, has been studied in PTSD with some evidence of efficacy,[61] but this has multiple effects aside from anti-inflammatory ones. Omega-3 PUFAs also have anti-inflammatory effects and have been studied in various psychiatric illnesses,[62] but less so in PTSD. One RCT of docosahexaenoic acid (DHA) in PTSD found no overall benefit, but a secondary data analysis showed that subjects with greater increases in erythrocyte membrane eicosapentaenoic acid (EPA) showed superior clinical responses.[63]

Because of the relative safety of several anti-inflammatories, we believe that RCTs of anti-inflammatories should be a high research priority in selected patients in PTSD. Specifically targeting patients with baseline immune over-activation could be important since, in MDD, infliximab, a TNF-α blocker, significantly ameliorated depressive symptoms only in the subgroup with elevated pretreatment inflammatory markers, although those without elevated baseline inflammation worsened.[33]

Mitochondria

The potential of pharmacologically inducing mitochondrial biogenesis has been suggested in a several somatic illnesses,[36] although this approach has not been studied in PTSD. As detailed in Figure 2, medications such as SIRT-1, 5-aminoimidazole-4-carboxamide riboside (AICAR), metformin, quercetin, resveratrol, bezafibrate, thiazolidinediones, and PQQ can increase mitochondrial biogenesis and also ameliorate MetS.[36,52,64–69] Angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs), which have proven efficacy in ameliorating hypertension, also increase mitochondrial biogenesis[70] and decrease inflammation in preclinical models,[71] and ARBs and ACE-Is have shown efficacy in improving depression and anxiety in humans.[71] One study in traumatized subjects showed that those using ACE-Is or ARBs had less severe PTSD symptoms than those who did not.[72] Nonetheless, there are few RCTs on the topic.

Another mitochondria-related target is oxidative stress. Several antioxidants (eg, L-acetylcarnitine, coenzyme Q10 [CoQ10], MitoQ10, PQQ, N-acetylcysteine [NAC], vitamin C, vitamin E, sodium pyruvate, and α-lipoic acid) have been proposed as therapeutic options for increasing mitochondrial functioning under conditions of inflammation or oxidative stress.[36] Certain psychological symptoms improved to a greater extent in war veterans (although not specifically with PTSD) taking 100 mg/day of CoQ10 than in those taking placebo.[73] Also, among veterans with PTSD and substance use disorders, those taking 2400 mg/day of NAC had greater improvements in PTSD than those receiving placebo plus psychotherapy.[74] One caveat in considering mitochondrial biogenesis activation, however, is that extensively upregulated mitochondrial mass may be detrimental rather than beneficial, suggesting an "inverted-U" type relationship.[10,34,35]

Gut Microbiome

Although no clinical studies, to our knowledge, have explored therapeutic options specifically based on the gut microbiome in PTSD, certain probiotics, prebiotics, and antibiotics have been shown to reduce symptoms of stress, anxiety, or depression in preclinical models,[75] in healthy subjects, and in individuals with irritable bowel syndrome or chronic fatigue.[75,76] In one preclincial study, vaccination with a heat-killed preparation of *Mycobacterium vaccae*, an immunoregulatory environmental microorganism, reduced PTSD-like symptoms[77] and was associated with an increased anti-inflammatory milieu. The relationship of the gut microbiome with metabolic dysregulation and inflammation highlights the intertwined relationship of several factors that may contribute to PTSD. Additional study is required to characterize gut microbiome changes and to determine if its modulation can benefit PTSD.[31]

Systems Biology

Additional targets of pharmacotherapy are suggested by network medicine approaches or mechanistic systems modelling approaches[78]. Network medicine identifies not only cellular mechanisms, but also how these mechanisms may span different diseases, thereby potentially identifying novel drug targets for seemingly unrelated diseases. Such approaches in the DoD "Systems Biology of PTSD" study suggested an association of glucocorticoid sensitivity with inflammation

and mitochondrial dysfunction, suggesting that modulating glucocorticoid receptor signaling may be effective in treating PTSD and concomitant somatic inflammation and mitochondrial dysfunction (Ibid.).

CONCLUSIONS

We have focused on inflammatory, metabolic, and mitochondrial dysfunctions, to the exclusion of several other pathogenic pathways, because they represent under-studied abnormalities in PTSD that may contribute to its pathophysiology and that are potentially remediable. These abnormalities are not seen in all individuals with PTSD, and conversely, these abnormalities are nonspecific, as they are also involved in other illnesses. We propose that inflammatory, metabolic, and mitochondrial dysfunctions, and perhaps gut dysbiosis, underlie certain somatic and neuropsychiatric aspects of PTSD in certain patients with PTSD. A critical consideration in designing future studies of the suggested novel interventions is identification of subgroups of patients with distinct and relevant biological perturbations.[33] Such interventions should target specific biological abnormalities rather than diagnostic criteria alone. To the extent PTSD comes to be seen as a systemic medical condition, or at least one with significant medical risks and comorbidities, stigma will decrease, objective biomarker testing will become available, and treatment focus will shift from purely psychological endpoints to treatment of the whole patient.

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