Review

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Biological Psychiatry

Metabolism, Metabolomics, and Inflammation in Posttraumatic Stress Disorder

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ABSTRACT

Posttraumatic stress disorder (PTSD) is defined by classic psychological manifestations, although among the characteristics are significantly increased rates of serious somatic comorbidities, such as cardiovascular disease, immune dysfunction, and metabolic syndrome. In this review, we assess the evidence for disturbances that may contribute to somatic pathology in inflammation, metabolic syndrome, and circulating metabolites (implicating mitochondrial dysfunction) in individuals with PTSD and in animal models simulating features of PTSD. The clinical and preclinical data highlight probable interrelated features of PTSD pathophysiology, including a proinflammatory milieu, metabolomic changes (implicating mitochondrial and other processes), and metabolic dysregulation. These data suggest that PTSD may be a systemic illness, or that it at least has systemic manifestations, and the behavioral manifestations are those most easily discerned. Whether somatic pathology precedes the development of PTSD (and thus may be a risk factor) or follows the development of PTSD (as a result of either shared pathophysiologies or lifestyle adaptations), comorbid PTSD and somatic illness is a potent combination placing affected individuals at increased physical as well as mental health risk. We conclude with directions for future research and novel treatment approaches based on these abnormalities.

Keywords: Animal models, Inflammation, Metabolic syndrome, Metabolomics, Neuroinflammation, PTSD

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Posttraumatic stress disorder (PTSD) is highly prevalent, with an estimate of prevalence among adult Americans to be 6.8% by the National Comorbidity Survey Replication (1). Rates vary greatly by characteristics of the individual and of the trauma, with rates generally higher after exposure to intentional, personally directed trauma as opposed to unintentional, nonpersonally directed trauma (2). Lifetime PTSD prevalence rates following combat trauma may be especially high, ranging from 10.1% to 30.9% in United States veterans (Vietnam and subsequent conflicts) (3–5). PTSD is precipitated by experiencing or witnessing actual or threatened death, serious injury, or violence, and it has manifestations that include reexperiencing, avoidance, negative thoughts or moods associated with the traumatic event, and hyperarousal (6). In addition to these traditional symptoms, individuals with PTSD, on average, have a substantially higher medical burden, with increased rates of cardiovascular disease, metabolic syndrome (MetS), diabetes, autoimmune diseases, and early mortality, suggesting widespread physical concomitants of PTSD (7–10). In addition to lifestyle-related factors (e.g., decreased physical activity, obesity, tobacco and substance use, medications) (11), certain processes intrinsic to PTSD pathophysiology have been proposed as contributing to somatic disease risk in PTSD, such as accelerated biological aging, sympathetic and glucocorticoid dysregulation, metabolic changes, inflammation, and others (12–17). Thus, PTSD might be considered to be either a systemic condition or one with significant systemic pathologies, rather than solely a mental illness or a brain disorder (9,12,13,18–21). This article is not intended to be an exhaustive review of the biology of PTSD. Rather, it is a selective overview of certain aspects of PTSD that have been under-studied, namely: 1) inflammation; 2) metabolic dysregulation; and 3) changes in circulating metabolites (especially those implicating mitochondrial dysfunction) that may play a role, not just in the medical disease burden but also in the core psychological symptoms of PTSD. Investigating these processes may reveal interconnected networks or pathways leading to the pathologies in PTSD or following in its wake (19,22–24). An important aspect of this article is the comparison of clinical and animal data for each of the processes we highlight, the latter being useful for mechanistic studies but limited by replicating only selected features of human PTSD. Methodological differences in the clinical studies include the severity and nature of the trauma (e.g., combat vs. civilian trauma, multiple vs. single exposure, interpersonal or intentional trauma vs. witnessed or nonpersonally directed trauma, psychological state, social support and coping abilities of the affected individuals, psychiatric and somatic comorbidities, recency of the trauma relative to the time of testing and source of recruitment of the study sample). Of particular importance in the preclinical studies are the ecological validity of the trauma, single versus multiple (or multimodal) trauma exposures and time of testing relative to the trauma exposure. Discussion of these and other methodological aspects are available for the interested reader

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(25,26). We conclude our review with a discussion of possible linkages between metabolomic, metabolic, and inflammatory abnormalities in this illness and with suggestions for novel treatments (Table 1).

INFLAMMATION

Clinical Studies

Human studies of PTSD have consistently found pronounced immune alterations, including increased concentrations of inflammatory cytokines and imbalances in immune cell proportions (27–32); these may increase medical morbidity and contribute to core symptoms of PTSD itself (29). In a recent meta-analysis of 20 studies (30), concentrations of interleukin-1β (IL-1β), IL-6, and interferon gamma (IFNγ) were significantly elevated in PTSD individuals compared with those of control participants. These remained significantly elevated after excluding individuals with comorbid major depressive disorder (MDD), although one study found elevated overnight serum IL-6 levels in individuals with PTSD plus comorbid MDD compared with levels in either control participants or those with PTSD alone (33). When only unmedicated participants were evaluated, these same cytokines plus tumor necrosis factor α (TNFα) were found to be significantly elevated in individuals with PTSD (34).

In one of largest studies exclusively in men exposed to combat trauma, those with PTSD showed a significantly elevated composite "proinflammatory score" comprising IL-1β, IL-6, TNFα, IFNγ, and C-reactive protein (CRP) levels compared with scores in those without PTSD (19). The individual cytokines whose levels significantly differed between groups included TNFα and IFNγ, with a trend for IL-6. The proinflammatory score remained significantly higher in individuals with PTSD after controlling for early-life trauma, MDD and its severity, body mass index, ethnicity, education, asthma and/or allergies, time since combat, potentially confounding inflammatory illnesses, and medications. Significant immune activation in PTSD was replicated by the same investigators in a separate group of combat trauma–exposed men (18).

The increase in inflammatory cytokines in PTSD is likely of clinical significance, since chronic inflammation can negatively affect cardiovascular and other aspects of physical health (7) and since individuals with PTSD are significantly more likely to suffer autoimmune disorders compared with individuals with other psychiatric diagnoses (9). Immune mediators, such as IL-1, IL-6, and TNFα, are able to cross the blood-brain barrier (35), and overproduction of proinflammatory cytokines can activate brain microglia (36,37). Nonetheless, the relationship of peripheral markers of inflammation to neuroinflammation is not clear (28,30,38,39). A few small studies have examined cerebrospinal fluid levels of cytokines in PTSD and have yielded conflicting results (40,41).

The underlying causes of immune activation in PTSD are not understood but may represent "sterile inflammation"; in other words, they may be related to diminished glucocorticoid levels (and/or altered glucocorticoid receptor sensitivity) and

Table 1. Hypothesized Druggable Targets in PTSD

Target and/or Process	Drug Mechanism of Action	Examples	References
Metabolism; Glucose and Insulin Regulation	Insulin and insulin sensitizers	Insulin (e.g., intranasal); metformin	(116,118,119,123–127)
	PPAR agonists	Thiazolidinediones; PPAR/PGC-1α activators	(128)
	Adiponectin upregulation	PPAR agonists; angiotensin receptor type I blockers; ACE inhibitors; cannabinoid receptor antagonists; thiazolidinediones; omega-3 fatty acids	(129)
Inflammation	Anti-inflammatories	Cortisol; TNFα antagonists	(42,52,53,130,131)
Mitochondrial Biogenesis and Energetics	PPARγ coactivator 1	Bezafibrate/fenofibrate; rosiglitazone/pioglitazone	(116,118,119,124,125,127,132–134)
	AICAR		(127)
	AMP kinase–activated protein kinase		(127)
	Sirtuins (SIRT 1 activator)	Quercetin; resveratrol; SRT1720	(127)
	Mitochondrial antioxidants	Coenzyme Q10	(133)
	Enhance ATP production	Creatine; lipoic acid; carnitine	(127)
	Trigger the NRF2 antioxidant response element	Oleanolic acid derivatives	(127)

Current pharmacologic treatment of PTSD is inadequate. The disordered processes presented in this article, if verified, would suggest novel therapeutics, such as insulin sensitizers, lipid regulators, mitochondrial biogenesis and/or function enhancers, and anti-inflammatories. Only the biochemical targets reviewed in this article are listed here. Many other potential targets exist. Trials with such agents could provide proof of concepts, especially if they are analyzed in conjunction with indices of target engagement. None of these classes of drugs is yet approved for treating PTSD, and their use would be investigational at this point. Current first-line approaches for most of these targets and/or processes involve aerobic exercise and caloric restriction and, to some extent, selective serotonin reuptake inhibitors. In any event, treatment of PTSD should involve improving physical as well as mental health; therefore, even if the approaches suggested here fail to ameliorate the core psychological symptoms of PTSD, their amelioration of physical disease and disease risk would be salutary.

ACE, angiotensin-converting enzyme; AICAR, 5-amino-imidazole-4-carbaxamide ribonucleotide; AMP, adenosine monophosphate; ATP, adenosine triphosphate; NRF2, nuclear factor erythroid 2–related factor 2; PGC, peroxisome proliferator–activated receptor γ coactivator; PPAR, peroxisome proliferator–activated receptor; PTSD, posttraumatic stress disorder; TNFα, tumor necrosis factor α.

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increased sympatho-medullary-adrenal activity as well as increased visceral adiposity, although this hypothesis remains to be adequately tested (29,42). It is also possible that the immune activation is related to microbial antigens (the gut microbiome), but further studies are needed (43–45). Longitudinal studies could assess directions of causality and determine whether the proinflammatory state follows the development of PTSD or whether it represents a preexisting risk factor for developing PTSD (29,42). One longitudinal study, the Marine Resiliency Study, showed that preexisting concentrations of CRP were directly correlated with the occurrence and severity of PTSD 3 months after a 7-month military deployment (adjusted for PTSD severity, trauma exposure, etc.) (46). In a study of civilian PTSD from orthopedic injury, elevated levels of IL-6, IL-8, and transforming growth factor β during hospitalization predicted the development of PTSD 1 month later (47). These data raise the possibility that immune dysregulation predisposes individuals to PTSD, although others disagree (20). Inflammation and PTSD could be either reciprocally related or indirectly rather than directly related, and connected via common mechanisms (28,29,42,48). Several studies suggest genetic and epigenetic mechanisms underlie aspects of the proinflammatory milieu in PTSD (49–51).

In summary, immune activation, along with possible imbalances in immune cell types, are among the most replicable biological findings in PTSD. Almost all clinical studies have assessed blood-based markers of inflammation; these may or may not be relevant to brain inflammatory activity. However, peripheral immune activation could contribute to the somatic illnesses seen in PTSD, although definitive routes or even directions of causality have not been proven. Results of studies predicting PTSD treatment response by baseline immune activation or by treatment-associated changes in immune activation have been inconsistent (28,30). Surprisingly few clinical studies have investigated whether primary treatment of immune abnormalities would improve PTSD symptoms (42,52,53). The one notable exception is treatment with hydrocortisone, which showed a therapeutic effect (52,53); however, mechanistic interpretation is difficult. In light of emerging evidence that immune blockade may benefit certain patients with MDD (namely, those with baseline evidence of immune activation) (54), immunosuppressant trials should be a research priority in selected patients with PTSD who show immune activation.

Preclinical Studies

Multiple animal models simulating features of PTSD have been developed and are discussed in the Supplement and in recent reviews (55–57). Inflammatory responses in animal models were seen in specific brain regions and throughout the system. A predator-exposure rat study found increased proinflammatory cytokines in the hippocampus, amygdala, and prefrontal cortex, with a concomitant reduction in anti-inflammatory cytokines (58,59). Similarly, a stress-enhanced fear-learning model showed increased hippocampal IL-1β concentrations, and the learning decrement was prevented by blocking central IL-1β signaling after the stress (60). In a predator scent–stress mouse model, activation of the pathway of the nuclear factor κ light-chain enhancer of activated B cells promoted anxiety, and inhibition of this pathway reduced both IL-1β concentrations and anxiety levels (61).

Molecular investigations found neuroinflammation to relate to behavioral manifestations of simulated PTSD in rodents (62). That study showed proinflammatory mediators (TNFα, CRP, IL-6, IFNγ, IL-1β, and cysteine-cysteine chemokine receptor type 2) upregulated in brain and spleen immediately and up to 4 weeks after stress withdrawal. These cytokines inhibited neurogenesis (62). Similarly, upregulation of haptoglobin, myeloperoxidase, and serum amyloid P-component in plasma samples indicated that there was inflammation resulting from aggressor-exposure stress (63). This indication was strengthened by the finding of elevated inflammation in liver and heart (64) immediately after aggressor exposure; this inflammation in the heart paralleled transcriptomic and histopathologic data, indicating cardiac susceptibility (64), which may have relevance for cardiovascular disease associated with human PTSD. Importantly, the kinetics of increased inflammatory responses have not been studied thoroughly, so it is unclear whether this response is sustained, and if so, for how long.

Animal studies have investigated the impact of anti-inflammatory therapies to alter PTSD-like features (65–70). In a rat model of psychogenic stress with elevated cytokine levels, treatment with minocycline, an anti-inflammatory, anti-apoptotic, and neuroprotective tetracycline agent, reduced levels of the cytokines IL-1, IL-6 and TNFα in the hippocampus, frontal cortex, and hypothalamus and reduced anxious behaviors (69). In another model with increased inflammation, ibuprofen not only decreased hippocampal expression of proinflammatory mediators TNFα, IL-1β, and brain-derived neurotrophic factor but also alleviated anxiety symptoms (68). A mouse foot-shock fear-conditioning study used treatment with cyclooxygenase-2 inhibitors, reducing a variety of stress-induced behavioral pathologies (65). Selective serotonin reuptake inhibitors, including fluoxetine, are considered first-line medication treatments for human PTSD. Using the foot-shock fear-conditioning mouse model (67), administration of fluoxetine improved PTSD symptoms while concurrently inhibiting stress-induced inflammatory gene expression (65,71).

Thus, the animal data, like the human data, support an inflammatory component of PTSD both systemically and locally in the brain, both on characterization of inflammatory mediator production and their inhibition.

METABOLIC SYNDROME

Clinical Studies

PTSD also is associated with a significantly elevated risk for MetS and for its individual components of obesity, insulin resistance and/or elevated fasting glucose, hypertension, and dyslipidemia (8,12,72). The presence of MetS is highly prognostic of future cardiovascular events and could contribute to the increased morbidity and mortality seen in PTSD (73). Markers of systemic inflammation have been proposed to be included in the definition of MetS, since increased CRP and IL-6 levels are correlated with individual components of MetS and they confer additional health risks beyond those ascribed to MetS alone (74,75). This interrelationship may have causal

elements, because inflammation can lead to obesity and insulin resistance (74), and since increased adiposity can lead to increased production of inflammatory cytokines including TNFα and IL-6. Supporting this interrelationship, Marsland *et al.* (75) studied inflammatory and MetS markers in 645 community volunteers aged 30 to 54 years (48% male, 82% European American, 18% African American), and found, using structural equation modeling, that a higher order common factor of MetS variables (especially adiposity) was significantly and positively correlated with inflammation (elevated CRP and IL-6).

One meta-analyses compared MetS prevalence in PTSD with that in participants from the general population and found an almost doubled risk for MetS with PTSD (relative risk, 1.82; 95% confidence interval, 1.72–1.92) (72); the pooled MetS prevalence for the PTSD group was 38.7%; abdominal obesity, 49.3%; hyperglycemia, 36.1%; hypertriglyceridemia, 45.9%; lowered high-density lipoprotein cholesterol, 46.4%; and hypertension, 76.9%. The prevalence of MetS in PTSD was independent of geographical region or population of participants (combat vs. noncombat PTSD, men vs. women, with vs. without comorbid MDD). A second meta-analysis (76) showed the pooled odds ratio (95% confidence interval) for MetS in PTSD compared with healthy control participants was 1.37 (1.03–1.82).

In a recent study of combat-related trauma in men (8) (with PTSD, $n = 82$; without PTSD, $n = 82$), the prevalence of MetS was significantly higher in individuals with PTSD (18.8% vs. 1.3%, $p < .0005$). The participants with PTSD showed significantly elevated homeostatic model assessment–estimated insulin resistance, fasting glucose concentration, and fasting insulin concentration, even adjusting for body mass index. These differences also remained significant after adjusting for tobacco use, comorbid MDD, and antidepressant use.

Thus, PTSD is associated with a significantly increased incidence of MetS and of its components, which may ultimately relate to the higher disease risk and mortality (12). Apart from contributing to somatic illness risk, MetS may also contribute to core psychiatric symptoms of PTSD, since increased fasting glucose levels and insulin resistance may be associated with damaging effects in the central nervous system (77,78).

While the direction of causality between PTSD and MetS, if any, is not known, Wolf *et al.* (79) examined MetS and PTSD in a longitudinal study and found that PTSD severity predicted subsequent increases in MetS after 2.5 years, but MetS did not predict subsequent PTSD. The causes of increased glucose concentration, insulin resistance, obesity, dyslipidemia, and hypertension found in PTSD are unclear, although increased inflammation, hypothalamic-pituitary-adrenal axis and sympathetic nervous system dysregulation, mitochondrial impairment, and metabolically active hormones (e.g., neuropeptide Y, leptin, adiponectin), as well as lifestyle changes (11,78,80), are possible (12,81–84). For example, Blessing *et al.* (8) found that insulin resistance, a hallmark of MetS, was directly correlated with pulse and the inflammatory marker CRP, although not with IL-6 or TNFα, suggesting a relationship for immune and sympathetic regulation. Polygenic risk for obesity (85) as well as early-life adversity (86) may also play a role in the interaction between MetS and PTSD.

In sum, PTSD is characterized by increased rates of MetS and of its components. When MetS is comorbid with PTSD, it may increase somatic illness comorbidity and possibly affect brain function.

Preclinical Studies

As with human studies, metabolic dysregulation of lipids was observed in several preclinical studies. Rats exposed to repeated python aggression showed delayed (6 weeks) decreases in "good" high-density lipoprotein cholesterol and sharp increases in serum triglycerides (a risk for cardiovascular disease) (87). In the resident–intruder model, mice exhibited features of MetS with weight gain (88), lipid dysregulation, and indicators of insulin resistance (63) plus activation of hormone-sensitive lipases leading to mobilization of lipids from adipose tissue, while carbohydrate and amino acid mobilization were suppressed. This was supported by increased activity in the liver, with the upregulation of lipid metabolism, fatty acid uptake, and lipogenesis. Human PTSD patients showed significantly reduced fatty acids and few differences in other lipid classes (metabolomics analysis) (18,19,23; Mellon *et al.,* Ph.D., unpublished data, December 2017), with increased levels of total cholesterol, triglycerides, and low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol levels (8).

Chronic psychosocial stress in mice also induced lipid dysregulation (89) and intrahepatic accumulation of triglycerides and indicators of MetS (90,91). In aggressor-exposed mice, changes associated with metabolic disorders also were observed by profiling transcripts in blood, brain, and spleen (62) and metabolites in plasma (63). The detection of 2-hydroxybutyrate, an indicator of insulin resistance and impaired glucose regulation, was significantly greater in the stressed mice, suggesting potential changes in insulin function (76,92).

Consistent with the human data (79), the animal literature also suggests that PTSD may predispose individuals to MetS (89,93–95), but data suggesting that MetS predisposes individuals to PTSD are scant (96). In sum, both human and animal data suggest a relationship between PTSD and MetS. The mechanisms (and causality, if any) remain unknown.

METABOLOMIC ANALYSIS IN PTSD

Many psychiatric and somatic diseases disrupt metabolism, resulting in long-lasting metabolic signatures for a particular disease. Metabolomics studies have the advantage of probing a very large number of metabolites, but personal lifestyle differences may add noise. Metabolomics data are most convincing when 1) identified metabolites interrelate in metabolic pathways and 2) results are replicated in separate samples of participants.

Clinical Studies

The first clinical study applying unbiased metabolomics using serum from PTSD cases showed glycerophospholipids and endocannabinoid signaling as potential pathologic pathways in PTSD (97). The Department of Defense–funded Systems Biology of PTSD study is the only other study utilizing an unbiased metabolomics analysis in PTSD (18,19,23; Mellon *et al.,* Ph.D., unpublished data, December 2017), and it included 164 combat trauma–exposed men: 82 PTSD cases and 82 control

participants. Data for these men were discussed previously regarding inflammatory markers (18,19) and MetS (8). Most of the metabolomics differences were found in energy-related pathways and in dysregulation of carbohydrate, lipid, and amino acid production and utilization. PTSD cases had increased plasma glucose levels and alterations in downstream glucose metabolites, shuttling toward much less efficient nonaerobic metabolism (extramitochondrial) versus aerobic (mitochondrial tricarboxylic acid [TCA] cycle–related) glycolytic pathways, which results in lactic acid buildup and inefficient energy production. Importantly, three separate intermediates of the TCA pathway (lactate, pyruvate, and citrate) showed coordinated changes in the PTSD participants, suggesting decreased entry of pyruvate into the mitochondrial TCA cycle. Also, PTSD cases had reduced plasma concentrations of many essential and nonessential fatty acids, including linoleate, linolenate, eicosapentaenoate, docosapentaenoate, and docosahexaenoate, as well as saturated and unsaturated fatty acids. The reduced abundance of some of these omega-3 fatty acids (docosapentaenoate, docosahexaenoate, and eicosapentaenoate) may contribute to insulin resistance and increased cytokine production as well as to cardiovascular disease (98) and reduced neuroprotective capacity (99). While the overall metabolic profile in PTSD pointed to inflammation, reduced energy utilization, and possibly mitochondrial dysfunction, the differences observed in levels of essential fatty acids may result from altered nutrient absorption or diet, issues with the gut microbiome, or differences in hepatic handling and metabolism of fatty acids.

Apart from metabolomic evidence, preclinical (reviewed below) and clinical studies have also suggested mitochondrial dysfunction in PTSD. Studies of human blood and postmortem brain samples (15,16) showed large numbers of dysregulated genes associated with mitochondrial function, many of which correlated significantly with the severity of PTSD symptoms. Among these, two common dysregulated pathways were found in PTSD: fatty acid metabolism (p = .0027) and peroxisome proliferator–activated receptors (PPARs) (p = .006). Additionally, mitochondrial DNA copy number, which is related to mitochondrial biogenesis, was positively correlated with positive affect ratings and was low in participants with combat-related PTSD (23). Mitochondrial DNA copy number is normally tightly regulated (100); hence, differences in the mitochondrial DNA copy number in PTSD participants may reflect dysregulation of this cellular process.

In sum, preliminary data from humans suggest the involvement of mitochondrial dysfunction in PTSD pathophysiology. The causes of possible mitochondrial dysfunction in PTSD are unknown but could be related to genetic or epigenetic factors, oxidative stress, cell damage responses, or premature cell aging, among others (101,102). The potential sequelae of mitochondrial dysfunction are extensive and include diminished fuel utilization and energy synthesis (e.g., anaerobic compared with aerobic respiration), altered glucose and lipid utilization, increased oxidative stress, cellular senescence and/or apoptosis (101–104), and others. It is possible that mitochondrial function may be a key target to prevent or reverse certain neurobehavioral and physiological aspects of PTSD (15,101,105,106) or may be directly related to immune activation and MetS in PTSD, as discussed below.

Preclinical Studies

A brain microdialysis metabolomics study in live mice enabled in vivo investigation of metabolites (at baseline) as predictors of subsequent sensitivity or resilience to PTSD-like behaviors in a foot-shock model (107). At day 2 after a stress event, behavioral symptoms (hyperarousal) in shocked mice were predicted by the enrichment of the TCA cycle and glyoxylate and dicarboxylate metabolism in the medial prefrontal cortex prior to foot shock. Another study also showed increased TCA cycle activity in synaptosomes of high-anxiety mice (108), suggesting that there may be inherent differences in functional synapses, which are enriched with mitochondria in control mice and high-anxiety mice.

The same investigators used proteomic and metabolomic analysis of specific brain regions in the foot-shock model to assess stress-induced dysregulated metabolic pathways after foot shock and to assess metabolic pathways that are responsive to treatment (fluoxetine). The stress led to decreases in TCA cycle pathway enzyme abundance and metabolites in the nucleus accumbens and the anterior cingulate cortex (66). Interestingly, fluoxetine treatment (12 hours after foot shock) prevented alterations of the TCA cycle in the nucleus accumbens and anterior cingulate cortex and decreased conditioned fear responses (66).

In a rat model of single, prolonged stress (109), ultrastructural examination of hippocampal neurons showed differential cellular organelle damage. Increased cytochrome oxidase release (mitochondrial) and enlarged and/or swollen mitochondrial structures with vacuolar and crest degeneration suggested mitochondrial damage.

Mice exposed to prolonged inescapable tail-shock stress showed induction of hippocampal apoptosis, suggesting involvement of mitochondrial pathways (16,110–113). Studies also found that 34 mitochondrial-focused genes were upregulated in the amygdala of stressed rats (16). As with humans, fatty acid metabolism and PPARs were among the 10 pathways found to be dysregulated. Finally, mitochondrial dysfunction, and the effects of risperidone and paroxetine on mitochondrial function, were studied in a rat model (114). Both drugs ameliorated stress-induced behavioral symptoms; risperidone ameliorated stress-induced increases in brain mitochondrial enzyme activities, and both drugs reduced stress-induced brain apoptosis, suggesting that both apoptosis and mitochondrial dysfunction may contribute to PTSD-like behavioral symptoms.

In summary, metabolomic changes in PTSD are understudied, especially in large clinical samples. Nonetheless, clinical and preclinical studies to date suggest that PTSD involves some aspects of mitochondrial dysfunction, and these may be related to the other abnormalities.

ARE INFLAMMATION, MetS, AND MITOCHONDRIAL DYSFUNCTION INTERRELATED IN PTSD?

In this review, we have highlighted inflammation, MetS, and metabolomic changes, especially those involving mitochondrial function, as potential individual pathologies in PTSD. However, these and other pathological features may be interrelated, although there is insufficient evidence to posit causal relationships. For example, mitochondrial dysfunction can lead

to reduced fatty acid metabolism (beta oxidation) and increased lipid accumulation in muscle and liver tissue, resulting in increased diacylglycerol, ceramide, and acylcarnitine accumulation and increased reactive oxygen species levels, all of which can lead to insulin resistance and further mitochondrial damage. Mitochondrial dysfunction can also result in increased inflammation via reactive oxygen species; reactive oxygen species trigger inflammasome (nucleotide-binding domain and leucine-rich repeat containing protein 3) activation, resulting in increased cytokine (e.g., IL1β and IL-18) levels. Nucleotide-binding domain and leucine-rich repeat containing protein 3 activation reciprocally regulates glucose and lipid metabolism. Central adiposity (and macrophages accumulating in adipose tissue) generates inflammatory cytokines (e.g., TNF) and inflammatory adipokines, leading to an inflammatory state seen with obesity and insulin resistance [see (22,115–120)].

Apart from these interrelationships, a "mitochondrial allostatic load" model has also been proposed to connect these perturbations (104). In this model, metabolic dysregulation and chronically elevated glucose concentration, as seen in PTSD, damage mitochondria and mitochondrial DNA, generating byproducts that promote systemic inflammation, alter gene expression and accelerate cellular aging. Lastly, mitochondrial dysfunction can affect cellular responses, suggesting "metabolic checkpoints" (121) or "cell danger responses" (101) that connect metabolism with mitochondrial function (121). In all of these models, mitochondrial dysfunction may be a "central link" between inflammation, oxidative stress, and metabolism, as suggested by Kusminski and Scherer (118).

A "systems biology" approach, assessing multiple features and levels of analysis in the same individuals, holds the greatest promise for delineating interlinked pathology, hopefully delineating biologically informed phenotypes, subgrouping, and diagnoses (122).

CONCLUSIONS

An accumulation of evidence suggests that PTSD has significant somatic manifestations and may, in fact, have aspects of a systemic illness or of an illness with significant systemic comorbidities. Any model of PTSD should, therefore, account not only for psychological symptoms but also for the physical morbidity and premature mortality seen in this illness. We have reviewed several, but far from all, systemic pathologies that may accompany PTSD, although it is not known how well these peripheral pathologies are reflected in the brain. Whether somatic pathology precedes the development of PTSD (and thus, may be a risk factor) or follows the development of PTSD (as a result of either shared pathophysiologies or of lifestyle factors), comorbid PTSD and somatic illness place affected individuals at increased health risk. Identification of novel mechanism-based treatment targets in PTSD holds promise for relieving both the psychological and somatic symptoms in this prevalent disorder.

To the extent the processes reviewed here participate in the pathophysiology of PTSD, new therapeutic opportunities, based on specific pathological targets, may exist. Certain such possibilities are listed in Table 1, but very few of these interventions have yet been tested. Even if the psychological symptoms of PTSD do not respond to these novel types of interventions, somatic health might improve and novel biochemical targets might be clarified.

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