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Traumatic stress, oxidative stress and posttraumatic stress disorder: neurodegeneration and the accelerated-aging hypothesis

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Abstract

Posttraumatic stress disorder (PTSD) is associated with elevated risk for a variety of age-related diseases and neurodegeneration. In this paper, we review evidence relevant to the hypothesis that chronic PTSD constitutes a form of persistent life stress that potentiates oxidative stress (OXS) and accelerates cellular aging. We provide an overview of empirical studies that have examined the effects of psychological stress on OXS, discuss the stress-perpetuating characteristics of PTSD, and then identify mechanisms by which PTSD might promote OXS and accelerated aging. We review studies on OXS-related genes and the role that they may play in moderating the effects of PTSD on neural integrity and conclude with a discussion of directions for future research on antioxidant treatments and biomarkers of accelerated aging in PTSD.

Posttraumatic stress disorder (PTSD) is a serious and often disabling condition that affects approximately 8 percent of the general population at some point during their lifetimes.[1] As many as one-third of individuals who experience a single episode of PTSD go on to develop a chronic form of the disorder that, in many cases, persists for years.[2,3] Comorbidity is common among these patients who often present with a complex combination of psychiatric and medical comorbidities including heightened risk for various age-related conditions including diabetes,[4] heart disease,[5] functional somatic syndromes such as fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome,[6] and neurocognitive disorders and dementia.[7,8] In this paper, we propose that chronic PTSD constitutes a form of persistent life stress and identify mechanisms by which it may potentiate oxidative stress (OXS) and accelerate cellular aging. Other recent reviews have addressed related topics, including the relationship between life stress and OXS in the brain,[9] the role of OXS in other psychiatric disorders and neurodegenerative disease (e.g., Hovatta *et al.*,[10] Li *et al.*,[11] and Palta *et al.*[12]), and the effects of psychological stress on aging.[13] However, to our knowledge, no prior review has focused specifically on the possible link between PTSD and OXS and the role of the latter in PTSD-related neurodegeneration and accelerated aging. Therefore, our primary goals in undertaking this review were to (1) provide an overview of empirical studies on the relationship between psychological stress and OXS, (2) advance hypotheses about how the

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stress-perpetuating symptoms of chronic PTSD might promote OXS and neurodegeneration, (3) review research on genetic moderators of these associations, and (4) discuss directions for future research.

Oxidative Stress: Concepts and Measurement

Oxidation is a chemical process ubiquitous in nature that involves the loss of one or more electrons from one atom to a second one known as an oxidant. Oxidants are introduced through endogenous processes such as the breakdown of glucose for energy by mitochondria or via external agents including chemical toxins, air pollution, and diet. Oxidant-promoting processes activate molecular signaling pathways that trigger the production of toxic free radicals and other potentially destructive reactive oxygen species (ROS).[14] These processes are regulated by a molecular defense system comprised of antioxidant enzymes and non-enzymes that maintain redox homeostasis and prevent cell damage. When levels of ROS and/or other pro-oxidant molecules exceed the capacity of available antioxidants to counteract their effects, OXS occurs. OXS is a fundamental molecular mechanism of aging and the organism's capacity to counteract it is essential to physical wellbeing, longevity, and survival.[16] OXS also triggers pro-inflammatory signaling pathways (and vice versa)[17,18] and is known to play a role in a variety of diseases including diabetes, cardiovascular illnesses, and neurodegenerative conditions.[16,17,19,20]

Of all the organs in the body, the brain is perhaps the most vulnerable to damage from OXS because of its high glucose and oxygen utilization and high concentration of peroxidation-susceptible lipid cells.[21] Consequences of OXS in the central nervous system include increased blood-brain barrier permeability, disruption of neurogenesis, impairment of synaptic plasticity, alterations of neurotransmission, and remodeling of neural morphology (for reviews, see Schiavone *et al.*[9] and Uttara *et al.*[22]). Aging is associated with increasing protein oxidation and diminishing levels of antioxidant enzymes in the brain[23] and these changes are potentiated by various disease processes. OXS is also implicated in neuronal death and erosion in neurodegenerative processes including prodromal dementia and Alzheimer's and Parkinson's disease.[24-30]

OXS can be measured using a variety of biomarkers—each with its own advantages and disadvantages—and detailed recent reviews of these methods are available.[31-35] In brief, the most common approaches aim to quantify either *antioxidant capacity* or the degree of *oxidative damage* present in a biosample. Antioxidant capacity refers to the ability of cells to counteract effects of oxidants and is estimated *in vitro*. Colorimetric and fluorometric probe assays can be used to measure the capacity of a sample to reduce oxidant molecules with the degree to which the oxidant agent changes color or fluorescence indexing the antioxidant capacity of the cells. The primary limitation of these methods is that the strength of association between in vitro measurement and in vivo antioxidant capacity is unknown. Alternatively, many studies have focused on biomarkers of *oxidative damage* to lipid, protein or DNA molecules. Oxidative damage to lipids can be estimated with assays for compounds called isoprostanes that are produced in vivo from peroxidation of lipid cells. F_2-Isoprostanes are widely used because they are chemically stable, specific products of peroxidation, present in detectable amounts in all normal tissues and bodily fluids, and

unaffected by lipid content in the diet. F_2-Isoprostanes have also been shown to increase substantially in animal models of oxidant injury,[34] and elevated levels have been observed in patients with various OXS-related diseases. Similarly, protein oxidation results in the introduction of carbonyl groups into proteins which can be indexed using protein carbonyl assays or mass spectroscopy.[35] One intriguing aspect of protein carbonylation research are the unique opportunities it for integrating data on protein modification with genomic and methylomic data to elucidate biological disease pathways spanning different levels of "–omic" analysis. At the genomic level, OXS-related DNA damage is commonly studied by examining oxidation of the DNA nucleobase guanine which yields 8-hydroxy-2′-deoxyguanosine (8-OH-dG) and 8-hydroxyguanosine; 8-OH-G). The primary limitation of this approach is that it offers only a global measure of DNA damage and cannot implicate specific genes or the amount of damage to a particular region of interest. Furthermore, regardless of which of these approaches is used, it is impossible to determine to what extent observed oxidative damage is due to the intensity of the ROS attack or the antioxidant capacity of the cell at the time of the attack. More clinical studies evaluating change over time in measures of both antioxidant capacity and oxidative damage in patients and controls are needed to clarify this complex interplay.

Psychological Stress and Oxidative Stress

Although, to our knowledge, no studies have directly examined the effects of trauma exposure on measures of OXS in humans, a growing body of research suggests that less severe psychological stress—especially chronic stress—promotes OXS throughout the body.[36,37] Elevated blood biomarkers of OXS have been found in chronically-stressed caregivers, with higher levels of perceived stress associated with higher levels of oxidative damage to RNA and lipid cells.[38] In one study, life stress at work and home was found to be a stronger predictor of suppressed antioxidant activity than other established oxidant-promoting factors such as cigarette smoking, alcohol consumption, poor diet, and exposure to ultraviolet radiation.[39] Elevated blood biomarkers of OXS have also been found in college students during periods of examination stress (e.g., Cohen *et al.*,[37] Nakhaee *et al.*,[38] and Sivonova *et al.*[41]) and in bereaved individuals following the loss of a spouse or close relative.[43] Another study showed that cortisol levels mediated the relationship between perceived stress and OXS damage in chronically stressed caregivers.[38] Links between OXS and various stress-related psychiatric diagnoses have also been found. For example, studies have shown that clinically depressed patients show elevated levels of oxidative DNA damage and suppressed antioxidant activity with the degree of damage covarying with depression severity even after controlling for behavioral factors.[44-47] Similarly, studies of patients with anxiety disorders have shown evidence of elevated lipid peroxidation in generalized anxiety disorder[48] and suppressed antioxidant activity in panic disorder.[49]

Animal models offer insight into potential mechanisms of association between psychological stress and OXS and, in turn, the effects of OXS on the brain. Oxidative DNA damage can be classically conditioned in rats through pairing of pain with administration of an oxidizing agent.[50,51] Further, prolonged restraint induces generation of ROS in peripheral blood cells and these effects can be partially reversed by anxiolytic agents.[52] Conversely, inducing ROS production through pharmacologic and non-pharmacologic methods produces

anxiety-like behavior in rats.[53,54] In one noteworthy study that featured a novel animal model of PTSD, Wilson and colleagues[55] studied effects of acute and chronic stress on OXS in rats using an extended 31-day stress protocol. Biomarkers of OXS and antioxidant activity were measured throughout the study and later in post-mortem analysis of brain and adrenal tissue. Compared to controls, rats in the stress condition exhibited slower growth, higher plasma corticosterone levels, greater anxiety-like behavior on an elevated plus-maze task, and a dose-response relationship between the duration of the protocol and levels of ROS. Post-mortem analysis of brain tissue revealed elevated levels of ROS and other byproducts of OXS in the hippocampus and pre-frontal cortex. Together, these findings demonstrate links between environmental stress and OXS and provide new insights into the effects of OXS on brain regions implicated in PTSD and other psychiatric conditions.

Mechanisms by which PTSD may potentiate Oxidative Stress and Neurodegeneration

Chronic PTSD is a stress-perpetuating syndrome characterized by hallmark episodes of sensory-memory reexperiencing of the traumatic event(s). Intrusions and flashbacks are accompanied by phasic activation of fear-related neurocircuitry,[56] elevated peripheral autonomic nervous system activity,[57,58] and enhanced cortisol and catecholamine output.[59-62] In some patients, reexperiencing symptoms occur quite frequently. For example, one study found an average of 30 intrusions per week in patients awaiting treatment.[63] Onset of intrusions can be spontaneous or triggered through exposure to stimuli reminiscent of the trauma,[64,65] anniversaries of the event,[66] or other adverse life events.[67] These events occur against a backdrop of tonic hyperarousal characterized by sleep disruption, hypervigilance, anger, and dysphoria. Furthermore, chronic PTSD tends to be associated with other psychiatric comorbidities, most commonly, major depression, and anxiety- and substance-related disorders.[68-70] Thus, in chronic patients, a condition that often begins as an acute anxiety reaction evolves into a pervasive and persistent illness with systemic impacts throughout the body—a form of persistent life stress—with possible consequences including neurodegeneration and other forms of accelerated cellular aging.

The notion that trauma is associated with accelerated cellular aging has a foundation in literature and historical observations dating back hundreds of years. One famous example was Marie-Antoinette whose hair reportedly turned white with fear the night before her execution by guillotine in 1793. This phenomenon, often associated with intense fear or grief, has been reified in the medical nomenclature as “Marie-Antoinette Syndrome.”[71] Interestingly, it is believed to occur when hydrogen peroxide produced by OXS in the hair follicle causes the hair to lose its pigment, i.e., “the free radical theory of graying.”[72] Jelinek[73] offered a fascinating review of this and other accounts of accelerated aging which together suggest that traumatic stress can render visible and permanent changes in the appearance of hair, skin, other physical attributes—all changes normally associated with aging, and all with established links to OXS.

HPA-Axis Activation

Though research on links between PTSD and OXS is in its infancy, evidence points to chronic and repeated activation of the HPA-axis (i.e., via reexperiencing of the trauma) as an important pathway. The HPA-axis is a key neurobiological substrate of the stress response. Abnormalities in its functioning have long been implicated in the pathophysiology of PTSD[74] and chronic and repeated activation of this system is understood as a primary mechanism of the deleterious effects of stress on the brain. The glucocorticoid-hippocampal atrophy model[75] posits that glucocorticoids released during stress exert neurotoxic effects on the central nervous system, with the hippocampus particularly vulnerable due to its high density of glucocorticoid receptors. Numerous animal studies have shown that elevated glucocorticoid levels are associated with increased ROS and oxidative damage. For example, Constantini et al[76] conducted a meta-analysis of 19 studies of vertebrate animals on effects of glucocorticoid administration on OXS parameters. Analyses revealed a mean effect size of $r = 0.55$ and also indicated that the longer the duration of glucocorticoid administration, the greater the oxidative damage. Other studies have shown that OXS is involved in mediating the effects of glucocorticoids on neurodegeneration. For example, Sato and colleagues[77] demonstrated that subcutaneous corticosterone administration induces lipid and protein oxidation and suppresses antioxidant enzyme activity in the rat hippocampus. These effects were associated with damage to pyramidal cells and neuronal cell death, which, in turn, were linked to memory impairment on a maze learning task. Similarly, corticosteroid treatment and chronic restraint stress have been shown to reduce antioxidant levels in the brain of rats.[78] Other animal studies that provide causal support for the role of glucocorticoids in OXS-related neurodegeneration have shown that glucocorticoids cause oxidative damage to neurons by increasing glutamate and calcium while decreasing antioxidant enzymes.[79,80] Thus, evidence points to chronic threat-related HPA-axis activation as an important mechanism of glucocorticoid-related OXS damage and suggest that these processes may be relevant also to PTSD.

Sleep Disturbance

Another process that may have bearing on the potential link between PTSD and OXS is sleep disturbance—a common symptom of PTSD that manifests as recurrent nightmares, restless sleep, and difficulty falling and staying asleep.[81,82] During sleep, neural activity, including glucose metabolism and oxidation processes, is reduced which tips the oxidant/antioxidant balance in favor of antioxidant processes. This is a fundamental mechanism of the restorative function of sleep and is supported by human studies that have found reductions in antioxidant agents and increases in OXS biomarkers following laboratory-induced sleep deprivation[83] and in patients with primary insomnia.[84] Sleep is increasingly recognized as essential to maintaining optimal neural functioning, detoxifying the brain, and stimulating neural restoration.[85,86] Prolonged periods of wakefulness result in the accumulation of ROS in the brain due to the high conversion of oxygen into energy needed to maintain wakefulness.[87] Animal studies have shown that sleep deprivation causes OXS in the hippocampus and deficits in memory and that these effects can be blocked with antioxidant agents.[88] Similarly, increases in anxiety-like behaviors and higher concentrations of OXS have been found in the cortex, hippocampus, and amygdala of rats

following sleep deprivation.[53] In sum, these studies suggest a causal link between sleep deprivation and OXS and indicate that sleep disturbance promotes OXS in the brain by interrupting elimination of free radicals, which, in turn, contributes to cognitive decline and neurodegeneration.

Neurodegeneration in PTSD

The foregoing is consistent with the hypothesis that chronic PTSD, through its impact on HPA-axis function, sleep deprivation, and likely other mechanisms as well, is associated with elevated OXS, and that over time, this condition may lead to neurodegeneration. Consistent with this, clinical structural neuroimaging studies have repeatedly found associations between PTSD and loss of neural integrity in the hippocampus, amygdala, medial prefrontal and anterior cingulate cortices (though there have been replication failures as well; for reviews, see Kuhn *et al.*[89] and Pitman *et al.*[90]). Furthermore, emerging research suggests that PTSD-related neurodegeneration may be linked to the duration and severity of the illness such that the longer an individual lives with PTSD, the greater the impact on neural integrity. Lindemer and colleagues[91] examined PTSD-related changes in cortical thickness using a novel index of the "cumulative lifetime burden" of PTSD reflecting both the duration and severity of illness. They found positive associations between this measure and reduction in cortical thickness in frontal, temporal, occipital, and insular regions. Similarly, other studies have found correlations between lifetime trauma load (i.e., total number of lifetime exposures) and reduced volume of cortical and subcortical structures.[92,93] Postmortem studies have implicated OXS in these changes. For example, Su et al[94] found 6 genes involved in the oxidative phosphorylation pathway to be differentially expressed in dorsolateral prefrontal cortex in post-mortem brain tissue of PTSD patients compared to controls. In sum, accumulating evidence suggests that PTSD, in its chronic form, is associated with neurodegeneration. We propose that this relationship may be explained, in part, by various OXS-promoting symptoms of the disorder, including repeated HPA-axis activation and sleep disturbance.

Genetic Factors, OXS, and Neurodegeneration in PTSD

The complex defense network of anti-oxidant enzymes and other molecules that respond to excessive accumulation of ROS is regulated by an equally sophisticated network of genes that confer individual differences in OXS response. Candidate gene and genomewide association studies (GWAS) in various species have linked numerous polymorphisms to OXS resistance[95] and twin studies in humans have found levels of peripheral biomarkers of OXS to be highly heritable.[96] Though OXS-related genes have been the focus of extensive research in neurodegenerative diseases, relatively few studies have examined their possible association with anxiety- or stress-related phenotypes. One important exception to this was a study by Hovatta et al[97] who examined gene expression levels across various brain regions in strains of mice that were genetically-modified to manifest different levels of anxious behavior. By experimentally manipulating OXS-related gene expression, Hovatta et al[97] showed that two genes that produce anti-oxidant enzymes (glyoxalase 1 and glutathione reductase 1) in the cingulate cortex modulated anxious behavior on several validated laboratory tasks. Subsequent animal studies have shown that the association between

glyoxalase 1 and anxious behavior may be mediated by methylglyoxal, a $GABA_A$ receptor agonist (the latter being the primary molecular target of the benzodiazepine class of anxiolytic drugs).[98]

Other evidence supporting a possible link between OXS-related genes and stress-related phenotypes came from a GWAS of PTSD, which implicated a gene with a known role in moderating OXS as a significant risk locus for the disorder. Logue et al[99] performed a GWAS using a sample of trauma-exposed veterans and their spouses and found a genome-wide-significant association between a SNP in the Retinoic Acid Orphan Receptor Alpha gene (*RORA;* rs8042149) and a diagnosis of PTSD in Caucasians. Subsequently, an independent research group published a replication of the rs8042149-PTSD association,[100] and in another study, Miller and colleagues[101] found that *RORA* SNP rs17303244 was associated with diagnoses of the fear spectrum (i.e., defined by panic, agoraphobia, specific phobia, and obsessive-compulsive disorders). Prior to this, *RORA* had been implicated in GWAS studies as a risk factor for various other psychiatric conditions including attention-deficit hyperactivity disorder,[102] bipolar disorder,[103] depression,[104] and autism.[105,106]

The RORA protein has four isoforms, one of which is expressed primarily in the central nervous system and found in cell nuclei in brain regions including the frontal cortex, hippocampus, and hypothalamus.[107] Its expression is activated during OXS,[108] and it protects neurons from apoptosis by increasing the expression of genes involved in the clearance of ROS (Gpx1 and Prx6).[109] Miller et al[101] hypothesized that the neurons of individuals carrying the *RORA* risk variant(s) mount an abnormal response to the OXS associated with PTSD, leading to neurodegeneration and functional abnormalities in regions of the brain subserving fear- and anxiety-related psychopathology. Consistent with this, *RORA* SNP variants have been linked in genetic-imaging studies to global measures of human cortical thickness and fractional anisotropy of cerebral white matter,[110] as well as to volume of the entorhinal cortex, the main interface between the hippocampus and neocortex.[111] Moreover, in the latter study, *RORA* SNPs were highly correlated with Alzheimer's disease-related atrophy. These findings point to the potential value of examining the role that *RORA* variants and other OXS-related genes play in moderating the effects of PTSD on neural integrity and brain morphology.

Directions for Future Research

Recent advances in the field of molecular genetics offer new directions for research into mechanisms of accelerated aging and its possible links to PTSD and OXS. Telomeres, which are nucleotide sequences located at the ends of chromatids that erode with normal aging as a result of repeated DNA replication, offer one potential metric of this process. Telomere shortening is accelerated by OXS through its effects on telomerase—an enzyme that maintains telomere length—whereas antioxidants decelerate telomere shortening and prolong telomerase activity.[112] Preliminary studies linking adverse life events[113,114] and PTSD to telomere shortening[115-117] point to the value of using telomeres in future research to measure accelerated aging in PTSD. For example, one recent cross-sectional study found lower relative leukocyte telomere length in veterans with probable PTSD than age-matched controls.[118]

DNA methylation profiling offers another approach. DNA methylation is the addition of a methyl group to the DNA base cytosine in regions known as CpG sites where a cytosine nucleotide occurs next to a guanine nucleotide (i.e., a *C—phosphate—G* sequence). Methylation in the promoter region of genes causes gene silencing and thereby represents a process by which gene expression is regulated. Methylation levels generally decrease with age, though certain regions show opposite effects. These processes are influenced by OXS via the oxidation of guanine in the CpG sequence.[119-121] Thus, as with telomeres, the methylation status of certain genetic loci can be used to index cellular age and the rate of cellular aging. In a landmark study on the development of an "epigenetic clock", Horvath[122] analyzed methylation data from 8,000 samples of 51 different tissue types and identified 353 sites that together offered a near-perfect predictor of age for non-cancerous tissues. Future studies of the accelerated aging hypothesis in PTSD may greatly benefit from the insights offered by this type of epigenetic clock.

In the treatment domain, an obvious direction for future research is to explore whether antioxidant compounds can prevent or slow OXS-related processes. Evidence supporting antioxidant supplements comes primarily from (a) in vitro studies demonstrating the antioxidant efficacy of Vitamins A, C, and E, (b) epidemiological nutrition studies showing the health benefits of antioxidant-rich diets (e.g., in reducing risk for Alzheimer's disease[123]), and (c) mouse models showing that antioxidant supplements reduce OXS-related mitochondrial damage.[124] A few clinical studies have also yielded positive results. For example, one randomized trial over 500 veterans with mild to moderate Alzheimer's disease found that vitamin E significantly reduced the rate of functional decline and decreased caregiver burden over a two-year follow-up period compared to placebo.[125] Unfortunately, the majority of human clinical trials of antioxidant therapeutics have shown little benefit or inconclusive results.

There are a number of plausible explanations for the gap between the promise of antioxidant therapies and the generally disappointing findings of clinical trials (for a review, see Firuzi *et al.*).[126] For one, it is likely that not all patients will benefit equally from antioxidant therapy. Given the substantial genetic individual differences in OXS reactivity, pharmacogenically-informed approaches may be needed to better match patients to specific antioxidant therapeutics. Another consideration is that most of the antioxidants studied operate globally with poor target specificity, whereas OXS damage may be limited to specific brain regions, cells types, or even certain membranes within cells. An antioxidant compound that offers a more targeted delivery is the mitochondria-targeted antioxidant SS31, which has been shown, in vitro, to protect neurons from neurotoxins.[127] Similarly, L-carnitine, which works as a free radical scavenger, readily crosses the blood–brain barrier[128] and has been found to reduce OXS damage in brain tissue, and enhance functional outcomes in patients with mood disorders, neurometabolic disorders, and Alzheimer's disease.[129-131] Thus, more targeted treatments and/or pharmacogenetically-informed approaches remain important directions for future intervention studies.

Caveats and Conclusions

We have reviewed evidence suggesting that chronic PTSD constitutes a form of persistent life stress that potentiates OXS and accelerates cellular aging. However, the evidence that led to this hypothesis is indirect and no studies have established a causal link between PTSD and OXS, or demonstrated that PTSD confers a greater risk for OXS and accelerated aging relative to other mental illnesses or stress-related conditions. Furthermore, we recognize though that OXS is just one of many possible molecular mechanisms for accelerated aging and note that other pathways such as pro-inflammatory signaling pathways that are reciprocally related to OXS are undoubtedly involved as well. We focused on OXS because, despite the evidence that we and others have laid out for its role in stress-related mechanisms of psychopathology and disease, it has received relatively little attention in the field of traumatic stress. In doing so, we hoped to elevate awareness of the relevance of OXS to PTSD and its comorbidities and to stimulate new research on accelerated aging in PTSD and other disorders of the trauma- and stressor-related disorder spectrum. Finally, given the seemingly ubiquitous role of OXS in aging and disease, it is untenable to conceptualize it as stress- or PTSD-specific mechanism. Rather, OXS is more appropriately viewed as molecular mechanism of disease and aging common to many illnesses but one that it may also be initiated or potentiated by traumatic stress, chronic PTSD and related conditions. As such, it represents a potentially useful avenue for future PTSD-related biomarker research and treatment development.

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