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Review

Chronic subordinate colony housing paradigm: A mouse model for mechanisms of PTSD vulnerability, targeted prevention, and treatment—2016 Curt Richter Award Paper

Stefan O. Reber[a,*], Dominik Langgartner[a], Sandra Foertsch[a], Teodor T. Postolache[b,d,e], Lisa A. Brenner[c,d,e], Harald Guendel[a], Christopher A. Lowry[c,d,e,f,g]

[a] Laboratory for Molecular Psychosomatics, Clinic for Psychosomatic Medicine and Psychotherapy, University Ulm, 89081 Ulm, Germany
[b] University of Maryland School of Medicine, Baltimore MD, MD 21201, USA
[c] Department of Physical Medicine and Rehabilitation, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045, USA
[d] Rocky Mountain Mental Illness Research Education and Clinical Center (MIRECC), University of Colorado, Anschutz Medical Campus, Denver, CO 80220, USA
[e] Military and Veteran Microbiome Consortium for Research and Education (MVM-CoRE), Denver, CO 80220, USA
[f] Department of Integrative Physiology and Center for Neuroscience, University of Colorado Boulder, Boulder, CO 80309, USA
[g] Center for Neuroscience, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045, USA

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ABSTRACT

There is considerable individual variability in vulnerability for developing posttraumatic stress disorder (PTSD); evidence suggests that this variability is related in part to genetic and environmental factors, including adverse early life experience. Interestingly, recent studies indicate that induction of chronic low-grade inflammation may be a common mechanism underlying gene and environment interactions that increase the risk for development of PTSD symptoms, and, therefore, may be a target for novel interventions for prevention or treatment of PTSD. Development of murine models with face, construct, and predictive validity would provide opportunities to investigate in detail complex genetic, environmental, endocrine, and immunologic factors that determine vulnerability to PTSD-like syndromes, and furthermore may provide mechanistic insight leading to development of novel interventions for both prevention and treatment of PTSD symptoms. Here we describe the potential use of the chronic subordinate colony housing (CSC) paradigm in mice as an adequate animal model for development of a PTSD-like syndrome and describe recent studies that suggest novel interventions for the prevention and treatment of PTSD.

Contents

Abbreviations: ACTH, adrenocorticotropic hormone; CD, cluster of differentiation; CpG, cytosine-phosphate-guanine; CRP, C-reactive protein; CSC, chronic subordinate colony housing; DSM-V, *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*; DSS, dextran sulfate sodium; GHC, group-housed control; GR, glucocorticoid receptor; HPA, hypothalamic-pituitary-adrenal; IBD, inflammatory bowel disease; IL, interleukin; IFN, interferon; LPS, lipopolysaccharide; NET, narrative exposure therapy; NF-κB, nuclear factor kappa B; OEF, Operation Enduring Freedom; OIF, Operation Iraqi Freedom; PBMC, peripheral blood mononuclear cells; PTSD, posttraumatic stress disorder; REM, rapid eye movement; SHC, single-housed control; TNF, tumor necrosis factor; Treg, regulatory T cells.

* Corresponding author at: Laboratory for Molecular Psychosomatics, Clinic for Psychosomatic Medicine and Psychotherapy, University Ulm, Albert–Einstein–Allee 23, 89081, Ulm, Germany.
E-mail addresses: stefan.reber@uniklinik-ulm.de (S.O. Reber), dominik.langgartner@uni-ulm.de (D. Langgartner), sandra.foertsch@uni-ulm.de (S. Foertsch), tpostola@psych.umaryland.edu (T.T. Postolache), lisa.2.brenner@ucdenver.edu (L.A. Brenner), harald.guendel@uniklinik-ulm.de (H. Guendel), christopher.lowry@colorado.edu (C.A. Lowry).

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1. Introduction

The estimated lifetime prevalence of posttraumatic stress disorder (PTSD) among adults in the United States is 6.8% (Kessler et al., 2005). However, estimates of current PTSD prevalence in military personnel deployed in two recent military conflicts, Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF), are up to three times than those in the general population, ranging from 13% to 20% (Seal et al., 2007; Vasterling et al., 2010). This is due to the fact that military personnel on active duty, by virtue of their profession and the daily risks in the performance of their duties, have increased exposure to the triggers of PTSD (Jones, 2006). PTSD prevalence may actually be even higher in this subgroup, as only 23% to 40% of service members and veterans in need of mental health services are estimated to access care (Hoge et al., 2004). The potential for further underestimation of real PTSD burden includes the stigma associated with PTSD diagnosis (Corrigan, 2004), as well as the perception that available treatments are prolonged and not always effective. A lack of reliable and easily accessible biomarkers and, thus, the failure to identify in a timely manner patients requiring treatment, is another barrier to effectively dealing with this condition and providing effective relief. In 2006, Dr. Tom Insel, then director of the National Institute of Mental Health, called for increased efforts to identify prevention strategies for PTSD and other mental health disorders (Insel and Scolnick, 2006). Although nowadays in developed countries there are effective treatment approaches for PTSD (Foa et al., 2009), up to 40% of PTSD patients do not reap all the benefits from individualized trauma-focused therapies (Bradley et al., 2005). Maercker and colleagues point out that there are at least millions of traumatized individuals in war-torn countries and regions (Maercker and Hecker, 2016). These authors also describe a substantial gap, particularly in poor countries, between the prevalence of mental disorders, including PTSD, and resources available for prevention and treatment (Collins et al., 2013). As a consequence, we may need more than mere individualized psychotherapy to treat such a high number of trauma survivors. Thus, there is a need for additional adequate animal models, with face, predictive and construct validity, which may help to discover additional effective treatment strategies for this complex disease, and may help to identify novel strategies for its prevention.

The burden of PTSD is further compounded by a number of comorbid conditions associated with it. Depression, alcohol and drug abuse, and high-risk behaviors, including suicide, are reported in more than 50% of veterans who suffer from PTSD (Hoge et al., 2004; Santiago et al., 2010). These patients also have an increased risk for autoimmune disorders, including thyroiditis, inflammatory bowel disorders, and rheumatoid arthritis (O'Donovan et al., 2015). The latter finding is consistent with recent genome-wide association studies identifying associations of PTSD with *ANKRD55* (Stein et al., 2016), a gene linked to several autoimmune and inflammatory disorders, including multiple sclerosis (Lill et al., 2013), type 2 diabetes mellitus (Harder et al., 2013), celiac disease (Zhernakova et al., 2011), and rheumatoid arthritis (Viatte et al., 2012). Furthermore, PTSD has an adverse effect on a variety of quality of life parameters, including physical health, shows high comorbidity with other mental impairments like anxiety disorders and affective disorders, and is associated with sleep dysregulation and cognitive deficits. These syndromes regularly lead to adverse outcomes including work-related impairment, further somatic illness, including cardiovascular diseases, and social and family strains (Boscarino, 2008; Cohen et al., 2009; Dirkzwager et al., 2007). Sleep disturbances, as a result of the reduced ability to fall and stay asleep, or increased frequency of nightmares, leading, in part, to disruption of sleep continuity, are of particular relevance, as they have a significant impact on PTSD symptoms and general functioning (Spoormaker and Montgomery, 2008). Re-establishing a healthy sleep pattern has been shown to have overall beneficial effects in depressed patients (Isaac and Greenwood, 2011) and to reduce PTSD symptom severity in PTSD patients (Spoormaker and Montgomery, 2008). PTSD, along with the comorbidities mentioned above, has a significant effect not just on patients but also on their families and caregivers, further adding to the burden of disease both socially and economically (Calhoun et al., 2002; Manguno-Mire et al., 2007).

2. PTSD characteristics according to the *Diagnostic and Statistical Manual of Mental Disorders*

In the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)*, released in 2013 by the American Psychiatric Association, PTSD was removed from the class of anxiety disorders and re-categorized into a new class of "Trauma- and Stressor-Related Disorders" (American Psychiatric Association, 2013), all requiring exposure to a traumatic or stressful event as a diagnostic criterion. In DSM-V, learning that a traumatic event occurred to a close family member/friend and experiencing first-hand repeated or extreme exposure to aversive details of the traumatic event were added to the list of witnessing or surviving life-threatening events. Moreover, DSM-V specifies in detail what constitutes a traumatic event. For instance, sexual assault and recurring exposure to the traumatic event have been added to the list, which were previously often excluded in the absence of exposure to actual or threatened death and serious injury. DSM-V further pays attention to the behavioral symptoms that accompany PTSD and, therefore, divides the cluster "numbing or avoidance" of DSM-IV into "avoidance" and "negative alterations in cognitions and mood", resulting in four distinct DSM-V clusters for the diagnosis of PTSD: re-experiencing, avoidance, negative cognitions and mood, and arousal, e.g. hypervigilance.

3. Issues related to symptom severity and thresholds for diagnosis and heterogeneity of PTSD subjects

Any discussion of animal models for vulnerability to a PTSD-like syndrome should be prefaced by the disclosure that PTSD is a human psychiatric disorder with a broad spectrum of well-defined behavioral symptoms, as currently outlined by DSM-V. Due to variability in the type and chronicity of traumatic experiences, and individual variability based on genetic, epigenetic, and environ-