Psychological stress is an Associated Health Risk to Military Exposures

Lindsay McDonald, PhD
Rocky Mountain Regional VA Medical Center

Funding Agency: VA ORD, BLR&D
CDA2 Award Number: BX004072
Over 300,000 Veterans have reported burn pit exposures on the AHOBPR as of March 2022

- 47.8% had respiratory disease
  - Greatest number of participants reporting symptoms are ages 35-44
  - most were in active duty army

Veterans are experiencing respiratory diseases at an increasing rate, & with earlier onset than civilians
Stress and mental health are important co-morbidities in multiple diseases however, our understanding of the direct impact of psychological stress on disease is limited.

**Chronic Stress and the Veteran Population**

- The second most reported condition among Veterans was Major Depressive Disorder (MDD) (2019 Post-Deployment Surveillance Report - data from over 12 million Veterans 2010-2019)

  - MDD, anxiety disorder, and PTSD were among the conditions that consistently had the highest incidence from 2015-2019 over all VHA users
    - in OEF/OIF/OND Veterans these conditions were even more prevalent

- Stress and mental health are important co-morbidities in multiple diseases however, our understanding of the direct impact of psychological stress on disease is limited
Veteran-centric Animal Model of Pulmonary Fibrosis

- Simplified Model
  - Development of Silicotic Nodules with Collagen Deposition
    - Heterogenous
    - Progressive, Non-Resolving

McDonald et al. inhalation Toxicology 2020

Adapted from www.Penncentury.com
Histological Features of Silica Exposure-Induced Pulmonary Fibrosis

- Increased collagen deposition 4-8 weeks post-instillation
- Development of fibrotic nodules
- Neutrophilic infiltrate

McDonald, et.al. Plos One 2017
Radiographic Features of Silica Exposure-Induced Pulmonary Fibrosis

A

Naïve  
Silica

In vivo Nitrogen

B

C

D

Redente et. al. PlosOne, 2023
Two-Hit Hypothesis for Pulmonary Fibrosis

- Hypothesis - Chronic stress is associated with early onset & increased incidence of respiratory disease
  - How does stress impact patient experience and mechanisms of pulmonary fibrosis?
Multiple models:

• Chronic Unpredictable Stress (CUS) - Mice are exposed to a variety of mild stressors daily

• Repeated stress – Forced Swim

• PTSD-like models – Combining stress with a “cue”
Stress Pathways

The Hypothalamic Pituitary Adrenal Axis (HPA)
- Glucocorticoids - Cortisol (Corticosterone)
- Dysregulation occurs in many who experience chronic stress

β-adrenergic system
- Catecholamines
- Epinephrine, Norepinephrine
- Fight or flight
Stress Signaling Pathways are Dysregulated in Mice Exposed to Chronic Unpredictable Stress

- Stress signaling through glucocorticoids is dysregulated as a result of 10 days of chronic unpredictable stress.

McDonald et. al. Frontiers of Psychiatry 2019
Experimental Design

Study Start

Chronic Unpredictable Stress

Disease Progression

Study Endpoint

1) Stress Exposures Begin
2) Silica Instillation

Four Cohorts: No Stress, Stress, Silica, Stress Silica
Behavioral Assessment – Open Field Test

**Anxiety**

- Increased time in periphery
- Decreased time in center
- Decreased mobility
Chronic Stress and Silica-induced Fibrosis Result in Anxious Behavior

- Increased time in periphery of the open field
- Decreased time in center
- Decreased mobility
  - Combined stress and silica exposure increase anxious behavior
Chronic stress leads to decreased bodyweight and slower recovery following silica-instillation

- Decreased bodyweight is associated with poor prognosis
- Lower bodyweight is independently associated with reduced survival in patients with pulmonary fibrosis

- Chronic stress may significantly impact patient outcome

- Decreased bodyweight is associated with poor prognosis
- Lower bodyweight is independently associated with reduced survival in patients with pulmonary fibrosis

- Chronic stress may significantly impact patient outcome
Chronic Psychological Stress Exacerbates Silica Exposure-Induced Pulmonary Fibrosis

- Chronic Stress Increases Collagen Deposition in Silica-induced Pulmonary Fibrosis

- **Massons Trichrome**
  - No Stress Silica
  - Stress Silica

- **Picrosirius Red**
  - No Stress Silica
  - Stress Silica

- **Collagen Staining**
  - No Stress Silica
  - Stress Silica

- **Picrosirius Red**
  - No Stress Silica
  - Stress Silica

- **Chronic Psychological Stress Exacerbates Silica Exposure-Induced Pulmonary Fibrosis**
Summary

Chronically stressed mice and mice with silica-induced pulmonary fibrosis exhibit:

• Anxiety and increased stress response
• Dysregulation of glucocorticoid signaling
• Decreased bodyweight
• Slower recovery following silica exposure
• Increased collagen deposition in fibrotic lungs (fibrotic response)

● In our animal studies, chronic stress results in physiological effects known to contribute to worse prognosis and decreased survival in patients
Elucidate mechanisms by which stress impacts pulmonary pathologies
- Glucocorticoids (HPA axis)
- β-adrenergic signaling
- Brain-Body Feedback Loop

Identify potential therapeutics for pulmonary fibrosis resulting from toxic exposures
- Increase understanding of mechanisms driving pulmonary disease
- Clarify guidance for use of corticosteroids toward personalized medicine

Identify patients for early monitoring and intervention
- Mental health screening for those identified as having experienced a toxic exposure

Improve awareness of the risks of mental health impact on lung disease
• RMR VA and PACT Act Symposium Organizers for the invitation and opportunity to share my research

• Veterans for their service to our country and contributions to research

• Mentoring Team
  • Dr. Dave Riches, PhD
  • Dr. Elizabeth Redente, PhD
  • Dr. Greg Downey, MD
  • Dr. Amanda C. LaRue, PhD
  • Dr. Howard Becker, PhD

• Funding, Department of Veterans Affairs, Career Development Award (CDA-2)