The Relationship between Neurochemistry, Stimulant Abuse, and Pharmaceutical Treatment Strategies in Combat-Exposed Military Veterans

Introduction

Although post-traumatic stress disorder (PTSD) is commonly seen throughout modern patients with medical complications, exposures to trauma, and dispositions to mental and physical abuses (Crum-Cianflone et al., 2016), much of its origin dates back to “shellshock” and the era of the soldier during World War I. Because of my background as a child of military service men and women, I find my interest in PTSD and its high prevalence in, and effects on, military veterans worldwide. Additionally, due to its deeply-rooted biological substrates in fear learning, the limbic and sympathetic nervous systems, and cognitive functioning, the disorder aptly applies to the Neuroscience of Fear. Over the course of the paper, I will analyze the neuroanatomy and pathogenesis of post-traumatic stress disorder, comparing and contrasting the neurological findings between related studies of patients with military- and combat-related PTSD. I will then compare findings on soldiers’ usage of prescription stimulants affecting the neuroanatomy of the brain during service, predisposing neural systems to the development of PTSD, and impacting soldiers’ neural and psychological functioning years after exposure to combat trauma. Lastly, I will investigate studies conducted on pharmacological interventions (including neurotransmitter reuptake and adrenergic inhibitors) to alleviate and potentially cure PTSD, contrasting the neurophysiological pathways involved and the effectiveness of each treatment method.

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Sub-Topic One: What is the Neuroanatomy of PTSD in Combat-Exposed Veterans?

Through combat experiences, killing enemies, and handling dead bodies, military men and women worldwide are exposed to risk factors (Crum-Cianflone et al., 2016) that predispose them to developing PTSD. Experiencing these traumatic events increases adrenergic (especially norepinephrine) levels (Griffin et al., 2014), activates the amygdala, and facilitates hippocampal memory consolidation of the event (Crum-Cianflone et al., 2016), resulting in soldiers' vivid, lasting memories of the occasion(s). Earlier studies conducted by Bremner et al. (1999) and Nitschke (2009) similarly detailed the activation of the amygdala involved in fear-processing and PTSD in soldiers. Using position emission tomography (PET) and traumatic images on Vietnam veterans to measure cerebral blood flow, both Bremner et al. (1999) and Nitschke (2009) found decreased flow to the ventromedial prefrontal cortex (vmPFC), which inhibits amygdala responsiveness. Without the normal functioning of the vmPFC, military men and women showed an increased activation of the amygdala (Nitschke, 2009), and thus, heightened consolidation of fearful memories. While Bremner et al. (1999) linked PTSD to reduced blood flow to the vmPFC, Butler et al. (2017) correlated the disorder with smaller vmPFC volume, decreasing in size as the duration of combat service increased. Although both studies drove different etiologies of PTSD, perhaps blood flow to, and volume of, the vmPFC are related, warranting more research in this field.

While Crum-Cianflone et al. (2016) identified only the heightened adrenergic levels and increased amygdala functioning in soldiers, Bremner et al. (1999) went a step further, detailing the patterns of increased blood flow to areas involved in memory and visuospatial processing, including the inferior parietal cortex, lingual gyrus, and posterior cingulate. This proposed an ensuing processing component to PTSD, not articulated by Crum-Cianflone et al. (2016). Further, Nitschke

(2009), using similar imaging techniques to Bremner et al. (1999), attributed less activity in the anterior cingulate cortex (ACC) of soldiers returning from Afghanistan and Iraq to PTSD. These findings add complexity to an already complex disorder, displaying the multitude of correlated brain regions and neurotransmitters involved in combat-related PTSD.

Sub-Topic Two: How does Stimulant Usage Affect PTSD in Veterans?

Despite the neuroanatomical similarities found between combat soldiers with PTSD, Crum-Cianflone et al. (2016) asserted that the disorder is not completely explained by these internal neurological factors. This team of researchers pointed to a potential link between the (forced) use of prescription stimulants (methylphenidate, dextroamphetamines, and amphetamines) to enhance alertness and increase cognitive performance in combat conditions, and a trending increase of PTSD among U.S. veterans. Obtaining and analyzing data through the Pharmacy Data Transaction Service (PDTS) and controlling for ADD/ADHD that warranted stimulant usage, Crum-Cianflone et al. (2016) found nearly five times the incidence of PTSD in research participants (soldiers) who took stimulants, compared to those who did not. Further evidence for stimulant ingestion and PTSD prevalence was described by Herbst et al. (2017). This team analyzed U.S. combat veterans who took 1, 3-dimethylamylamine (DMAA), a sympathomimetic amine stimulant found to improve strength and performance, and detailed the increased onset of PTSD symptoms (Herbst et al., 2017). Specifically, Herbst et al. (2017) highlighted experiences of hyperarousal, panic, and insomnia suffered by PTSD patients, not explained by Crum-Cianflone et al. (2016). Using a more subjective survey tool with fixed-response and multiple-choice questions, Ramirez et al. (2013) reported similar findings of PTSD in stimulant-misusing patients who were awaiting care in an American military tertiary care hospital. The researchers also reported a higher likelihood of deployment-

related injury in combat patients who used stimulants and a trend among younger patient cohorts (deployed to combat situations within the last five years) in the use of stimulants (Ramirez et al., 2013), not found by Crum-Cianflone et al. (2016), nor Herbst et al. (2017).

Unlike the three studies conducted on American veterans, Odenwald et al. (2009) discovered a link between chewing khat leaves (which contain the amphetamine-like substance, cathinone) and PTSD in Somalian armed forces: those who used khat more frequently reported higher rates of PTSD. While Crum-Cianflone et al. (2016) made use of the American PTSD Checklist-Civilian Version to diagnose the disorder, Odenwald et al. (2009) utilized the Somalian Posttraumatic Stress Diagnostic Scale, depicting a potential cross-cultural dynamic of stimulant usage affecting PTSD. Despite variances in the nature of the stimulant (artificial vs. natural) and the diagnostic methods involved, Odenwald et al. (2009), Crum-Cianflone et al. (2016), Herbst et al. (2017), and Ramirez et al. (2013), collectively found similar increases in PTSD among military subjects, expressing the prevalence of stimulant-intake among military veterans with PTSD and detailing its role in increasing norepinephrine in the brain. The varied research supports the findings of Crum-Cianflone et al. (2016) – that combat trauma heightens adrenergic levels to create longer lasting, fearful memories of traumatic events. From here, research may then be conducted to understand the role of pharmaceuticals in the treatment of the adrenergic connections in those with combat-related PTSD.

Sub-Topic Three: What Pharmaceutical Treatments Work for Veterans with PTSD?

Although 89% of veterans currently receive selective serotonin reuptake inhibitors (SSRIs) and other anti-depressants to treat symptoms of PTSD, only 20% of these patients are effectively treated, and the majority drop out of treatment within five years (Alexander, 2012). While an Austrian study reported the statistical effectiveness of fluoxetine, a recommended first-line SSRI (American Psychiatry Association), in reducing acute trauma symptoms and minimizing relapse in veterans with PTSD (Martenyi and Soldatenkova, 2005), a similar placebo-controlled, randomized clinical trial conducted on combat veterans with severe, chronic PTSD yielded a 17% effectiveness of fluoxetine in treating acute symptoms, as compared to a 33% effectiveness in the placebo control (Hertzberg et al., 2011). These contrasting findings, amongst a wealth of other conflicting studies, detail the variance in the effectiveness of SSRI treatments in veterans with chronic, combat-induced PTSD, and further support the statistics gathered by Alexander (2012) of their success in *non-*

combat-related PTSD. Thus, there is a need to turn to other pharmaceuticals to provide combat veterans with more effective treatment in modifying fearful experiences and diminishing PTSD.

Through the use of placebo-controlled, double-blind crossover protocols, several studies evaluated the efficacy of prazosin, a centrally-active adrenergic antagonist, in decreasing the severity of PTSD symptoms in combat veterans (Raskind et al., 2003; Thompson et al., 2012; Koola et al., 2014). Prazosin directly inhibits the action of epinephrine and norepinephrine at adrenergic receptors, lowering levels of these catecholamines in the body (Raskind et al., 2003). Raskind et al. (2003), Thompson et al. (2008), and Koola et al. (2014) found prazosin to be effective in decreasing the severity of PTSD symptoms (including nightmares and distress) and increasing functional status in combat veterans. This directly coincides with the research conducted by Crum-Cianflone et al. (2016), affirming the role of norepinephrine in the consolidation of traumatic, combat-related memories, and suggesting the contribution of brain adrenergic activity in both nightmares and general distress amongst patients with PTSD (Thompson et al., 2008). Through the study of adrenergic antagonists and other pharmaceuticals that target the neurochemical pathways involved in combat-induced PTSD, military veterans worldwide may soon see greater, individualized benefits in the quality, duration, and outcome of their care.

Conclusion

Due to their involvement with the adrenergic system and fear consolidation (Crum-Cianflone et al., 2016), both stimulants and adrenergic-antagonists play a role in combat-related PTSD amongst military service men and women. By using this same pathway, stimulant intake increases the levels of norepinephrine in the brain and results in higher rates of PTSD in veterans (Odenwald et al., 2009; Ramirez et al., 2013; Herbst et al., 2017). Targeting the neurotransmitters involved in these fear systems, antagonist medications better alleviate symptoms of PTSD in prior soldiers, as

compared to SSRIs (Raskind et al., 2003; Thompson et al., 2008; Hertzberg et al., 2011; Koola et al., 2014). These topics connect with the PTSD pathology unit of Neuroscience of Fear (including PTSD in ICU patients), address the etiologies behind the increasing rates of clinically-disordered veterans, and provide potential treatment methodologies to alleviate their suffering.

Future Perspectives

Because of the dearth of current research on military members' usage of performance-enhancing stimulants in combat situations (including the concurrent usage of stimulants in military service men and women), more studies must be conducted to better understand the pathogenesis of PTSD, the neurochemistry involved in stimulant usage, and the effects of stimulant usage on fearful responses to combat. If the military is going to continue to force these stimulants upon their soldiers, it is only fair to employ scientists to uncover the full effects of these medications on their recipients. Furthermore, additional research is necessary to assess the interaction between pathophysiology, genetic predispositions, and epigenetic-environmental factors involved in PTSD. Then, scientists and physicians may better tailor pharmaceutical treatment plans alongside psychological therapies to ensure the highest quality care for military veterans afflicted by PTSD.

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