Dual Sympathetic Block (LEVEL 4)
DSB FOR PTSD

Introduction

Post-Traumatic Stress Disorder (PTSD) is a disabling psychiatric disorder associated with functional and cognitive impairments which results following exposure to real or perceived physical or mental injury or threat (1). PTSD is characterized by re-experience and avoidance symptoms such as intrusive thoughts, nightmares, flashbacks, dissociation, intense negative emotions, problems with sleep and concentration, irritability, increased reactivity, increased startle response, and hypervigilance (1). As PTSD is one of the strongest correlates of suicidal ideation, lifetime suicide plans, and suicide attempts, PTSD has profound implications at the individual-level and the global health-level (2-3). PTSD can significantly impair individual, social and family functioning and high rates of PTSD comorbidity with depression, substance abuse disorders and physical health problems ultimately result in poor individual-level outcomes (1).

Although PTSD was initially publicized in association with United States military deployment in Afghanistan and Iraq, PTSD can affect any individual exposed to traumatic events, such as natural disasters, physical assault, exposure to stressful situations related to the COVID-19 Pandemic, and childhood or domestic abuse. Prior to the COVID-19 Pandemic, epidemiological studies reported estimated overall lifetime PTSD prevalence rates of 6.2-8.2% for men and 13.0-20.4% for women (4). A recent meta-analysis demonstrated an estimated PTSD prevalence of 17.52% amongst COVID-19 survivors, health professionals, and the population at large following the onset of the COVID-19 Pandemic (5).

Risk Factors for PTSD

Research suggests that approximately one third of individuals who experience a severe traumatic event will develop PTSD (6). Certain sociodemographic and psychiatric factors have been associated with an increased risk of developing PTSD following a traumatic event, such as history of physical or psychiatric disorders, cumulative exposure to traumatic experiences, and co-occurrence of other psychiatric disorders like Generalized Anxiety Disorder (GAD) or Major Depressive Disorder (MDD) (6-7). Further, genetic and epigenetic factors may account for up to 70% of the individual differences in PTSD development (8). In addition, specific features of traumatic events can influence risk of developing PTSD. As such, interpersonal violence generally leads to higher rates of PTSD compared to exposure to other traumatic events (i.e. natural disasters, death of loved ones, etc) (4).

Current Treatments for PTSD

Conventional first-line PTSD treatment protocols include trauma-focused cognitive behavior therapy (i.e. “talk-therapy”, prolonged exposure therapy, eye movement desensitization and reprocessing, and other evidence-based modalities) usually in combination with pharmacological interventions (i.e. antidepressants, antipsychotic drugs, and/or mood stabilizers) (1, 9). Although some patients may find these conventional treatments adequate for symptom relief or even symptom remission, many patients with PTSD continue to struggle managing their symptoms despite seeking care. At present, only 2 medications, paroxetine and sertraline, are approved by the US Food and Drug Administration for the treatment of PTSD (9). Despite FDA approval, these selective serotonin reuptake inhibitors may provide suboptimal symptom relief for at least a subset of PTSD patients, specifically those with comorbid psychiatric disorders (9).

PTSD Pathogenesis

Despite many known risk factors for developing PTSD, the exact molecular mechanisms leading to PTSD pathogenesis remain ill-defined. Research indicates that traumatic exposures activate the stress response pathways of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system (SNS) (4). HPA and SNS stress responses are orchestrated by neuroendocrine signaling between the autonomic nervous system (ANS) and target organs in the periphery (10). The two branches of the ANS are responsible for producing antagonistic physiological effects, and the ganglia associated with the ANS essentially act as a junction between the nerves originating from the central nervous system and the nerves innervating their target organs in the periphery. The sympathetic ganglia deliver information to the body about stress, impending danger and fear. These ganglia are responsible for eliciting physiological responses to these stimuli, commonly known as the “fight-or-flight” response. Alternatively, the parasympathetic ganglia produce antagonistic physiological responses in order to maintain a steady-state, commonly known as the “rest-and-digest” response (10). The stellate ganglion (SG) is a nerve cluster associated with the sympathetic nervous system. The SG is located in the upper neck and functions to coordinate with the central nervous system to produce sympathetic physiological responses. Signals from the SG are transmitted to a wide range of peripheral targets, including the heart, eyes, sweat glands, and pain receptors (11-13). As such, the SG has a major role in carrying out sympathetic nervous system responses. In healthy, normally functioning individuals, “fight-or-flight” responses are associated with appropriate stimuli, such as an increase in sweating and heart rate when running from a bear or while slamming on the brakes to avoid a car accident. Further, mental or emotional stress has been shown to stimulate the sympathetic nervous system and elicit similar physiological responses to physical stress (14-16). The sympathetic

nervous system is essential to normal functioning and survival because these physiological responses liberate extra energy and equip the body to deal with emergency situations. Despite this vital role, overstimulation of the sympathetic nervous system can therefore lead to dysfunctional or inappropriate physiological responses (17).

Unfortunately, the physiological manifestations of sympathetic stimulation do not exclusively occur as a response to appropriate stimuli for individuals with PTSD (10). Research has evidenced that patients with PTSD exhibit overactive sympathetic reactivity and activity both during mental stress and under resting conditions (2-4). Clinical manifestations of overactive sympathetic reactivity include hyperarousal, heightened physiological responses to stressors and increased startle responses, all of which are also characteristic PTSD symptoms (13-14). Additionally, overactivation or inappropriate activation of the SNS results in abnormal release of glucocorticoids and catecholamines. Elevated levels of glucocorticoids have been widely accepted to have immunosuppressive effects and to have downstream effects on negative feedback inhibition of the HPA axis (4). As such, abnormal release of glucocorticoids following exposure to traumatic events can lead to changes in neuroendocrine functioning (via increased glucocorticoid binding to glucocorticoid receptors) which maintains a hyperactive sympathetic state (4). Multiple peer-reviewed publications have described evidence suggesting that recurrent trauma-related symptoms experienced by PTSD patients arise from enhanced, prolonged, and/or inappropriate activation of the SNS stress response (18-20).

Among the various physiological abnormalities hypothesized to contribute to PTSD pathophysiology, autonomic dysfunction is especially noteworthy due to the widespread influence of the autonomic nervous system. For instance, animal studies have demonstrated that repeated stress signaling in PTSD can elicit neural growth in the basolateral amygdala, causing alterations in hippocampal activity (21-22). The sympathetic nervous system is closely linked through a poly-synaptic connection from the stellate ganglion to the amygdala and hippocampus, which are two brain structures with established roles in modulating PTSD symptoms (22). Neural growth both in the basolateral amygdala and the stellate ganglion is driven by the activity of nerve growth factor (NGF) following acute and chronic stress (23). As such, these functional abnormalities may promote a dysfunctional SNS state observed in PTSD (22). Further, PTSD is associated with increased concentration of norepinephrine in cerebrospinal fluid (23). Norepinephrine is a hormone with an established role in the SNS to execute physiological responses following SNS stimulation (23). Animal models of PTSD indicate that increased NGF activity in response to repeated stress signaling results in sympathetic nerve sprouting at the stellate ganglion and subsequent elevation of cerebrospinal fluid concentrations of norepinephrine (23-26).

Dual Sympathetic Block for PTSD

Recent neuroscience research has revealed a new therapeutic avenue for individuals with PTSD: Dual Sympathetic Blocks (DSBs). DSBs are a specialized sympathetic nerve block in which local anesthetic is injected into the right cervical sympathetic ganglion during the first appointment and the procedure is repeated on the left cervical sympathetic ganglion during the second appointment, reducing the concern of phrenic and recurrent laryngeal nerve palsy. Unilateral selective blockade of cervical sympathetic ganglions are commonly referred to as Stellate Ganglion Blocks (SGBs), and DSBs are essentially bilateral SGBs. For many years, DSBs have been safely used as a minimally-invasive treatment option for various autonomic nervous system-related medical conditions (27-28). More recently, however, DSBs have been shown to provide significant and long-lasting PTSD symptom relief, including anxiety, negative mood, and hyperarousal (29-34). When used in conjunction with trauma-focused psychotherapy, SGBs have been shown to have a 70%-80% success rate in treating PTSD symptoms (29-34). Results from a randomized control study support a strong efficacy profile of SGBs for PTSD as the improvement in CAPS-5 total symptom severity scores was twice as large in the SGB group compared to the sham group (34). At present, there are four ongoing clinical trials investigating the impact of selective blockade of cervical sympathetic ganglions on PTSD.

Across various clinical reports, selective blockade of cervical sympathetic ganglions have been demonstrated to significantly reduce PTSD symptoms (29-34). Results from a multisite, blinded, sham-procedure, randomized clinical trial that investigated the effect of paired right-sided SGB on PTSD symptoms indicate that patients who received the procedures had significantly improved scores on assessments of PTSD (improvement of 10 or more points on mean CAPS-5 total symptom severity scores from baseline to 8 weeks) compared with patients receiving sham procedures (34). Similarly, a recent clinical case study (32) involving 166 active duty service members reported that over 70% of study participants experienced a significant reduction of PTSD symptoms following a right-sided SGB as measured by an improvement in PCL-4 scores compared to baseline. Furthermore, of the 166 patients who received a SGB, 70% had a clinically significant improvement in PTSD symptoms which persisted beyond 3 to 6 months post-procedure (27). Results from a recent retrospective analysis of 327 consecutive cases of patients diagnosed with PTSD in various cohorts who were treated with cervical sympathetic blockade showed a statistically equivalent clinical benefit regardless of psychiatric variables (i.e. a history of suicide attempts or use of psychiatric medications) (35). These results support the use of cervical sympathetic block in the treatment of PTSD in both military populations and most populations with heterogeneous psychosocial backgrounds (35).

Proposed Mechanism of DSB

Excessive NGF signaling following trauma exposure may contribute to norepinephrine-mediated hyperactivation of the stellate ganglion, leading to development and/or maintenance of autonomic PTSD symptoms (e.g. increased baseline heart rate and blood pressure, hyperarousal, anxiety) (23-26). Although the exact mechanism by which DSBs alleviate PTSD symptoms is unknown, it has been hypothesized that DSB may block trauma-induced nerve growth in the stellate ganglion, which may subsequently reduce norepinephrine activity in the poly-synaptic network between the stellate ganglion and amygdala, effectively reducing sympathetic-related PTSD symptoms (23-26, 25).

Limitations of DSB for PTSD

Conclusion

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