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Modulation of NGF by cortisol and the Stellate Ganglion Block – Is this the missing link between memory consolidation and PTSD?

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ABSTRACT

Post-Traumatic Stress Disorder (PTSD) is a common psychiatric disorder that is often associated with intrusive memories and deficits in declarative memory function. The neurobiology of this effect is complex. The report focus is to provide an overview of systems activated during stress and consequences of the activation as well as modulation of those effects. Two systems predominate in stress and related memory processing and encoding. They are the autonomic nervous system (ANS) and hypothalamic–pituitary-adrenal axis (HPA) axis. ANS has significant effect on enhancing encoding of emotional memories, sensitization, and fear conditioning with the main neurotransmitter being norepinephrine (NE). HPA system is involved in memory regulation where cortisol (CORT), by itself and with NE, regulates memories of emotional events. Therapeutic interference with stress-related memory dysfunction has been a focus of research for some time. New focus of this research may be the HPA axis and ANS. Recent evidence demonstrates significant efficacy in prevention of PTSD by administration of CORT, as well as treatment of PTSD by utilization of Stellate Ganglion Block (SGB), which reduces NE. Both therapeutic approaches may act by a common pathway involving Nerve Growth Factor (NGF). This factor may be the "missing link" between memory consolidation and PTSD. Suppression of NGF can reduce memory effect directly or by effect on NE, leading to prevention or effective treatment of PTSD.

Overview of Post-Traumatic Stress Disorder (PTSD) occurrence and impact

Post-Traumatic Stress Disorder (PTSD) is a very common psychiatric disorder that is often associated with intrusive memories and deficits in declarative memory function. The rate of effected personnel depends on the population. The PTSD rate in military personnel has been quoted as approximately 14–35% of our 22.8 million US veterans with a history of combat duty, a figure that far surpasses the 6.8% prevalence of PTSD among non-combat veteran adult Americans [1]. Additionally, nearly 1 in 5 (18.3%) of US women have been sexually attacked [2]. Most of these female victims, (79.6%], experienced their first sexual attack before the age of 25, and 42.2%, experienced their first sexual attack before the age of 18 [2]. A lifetime prevalence for PTSD of more than 50% has been observed among women who have been sexually assaulted [3].

Considering the rate of occurrence of PTSD in the military and civilians, the need to prevent and treat PTSD cannot be over stated. To that end, further elucidation of mechanisms responsible for initiation and maintenance of PTSD are important for the development of approaches to prevent and treat this devastating disease. Multiple approaches have been tried in combating this psychiatric disorder, among them being medications, virtual reality exposure therapy, Yoga etc. A time has come to perhaps focus on the biology of stress and its effects. Trauma can modulate various mediators and neurotransmitters that, in turn, can produce clinical changes in the brain leading to clinical manifestation currently called PTSD. Hypothesis presented below will focus on a limited number of various mediators and neurotransmitters affecting the brain, with primary focus on memory. Clinical evidence as well as therapeutic implications are also presented.

Summary of previously reported evidence and the hypothesis of PTSD prevention and treatment

Overview of PTSD with focus on memory

PTSD is a chronic anxiety disorder caused by perceiving or experiencing traumatic events. One of the most prominent symptoms of PTSD includes re-experiencing the event through flashbacks or nightmares connected to the memory disturbances.

Memory disturbances, such as disruptive, vivid, emotional, and somato-sensory-intrusive memory, play a key role in the development and maintenance of Post-Traumatic Stress Disorder (PTSD)

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[4]. Beyond the above symptoms, memory dysfunction has been shown to be associated with PTSD [4]. This has been highlighted in a follow-up study of veterans of World War II that showed many people still suffered from episodes of 'black-outs' or loss of explicit memory by Archibald in 1965 [5].

The key processes underlying memory pathways involved in PTSD are primary consolidation of the initial trauma memory into long-term traces, as well as recurrent cue-triggered reactivation [4].

Review of memory consolidation and PTSD development

Disruptive, vivid, emotional, and somato-sensory-intrusive memories are hallmarks of PTSD [6]. The key processes underlying this pathway are: (1) the primary consolidation of the initial trauma memory into long-term traces, and (2) its recurrent cue-triggered reactivation. Memory is affected by a number of systems that are activated during severe stress. The two most prominent systems are hypothalamic-pituitary-adrenocortical (HPA) axis, with CORT being the most prominent active agent, and autonomic nervous system (ANS), with norepinephrine (NE) being most prominent agent. Concentrations of ANS mediators (norepinephrine) surge during acute stress and have been shown to persist following the acute stress in PTSD patients [7]. The amygdala is activated by stress hormones, leading to increased emotional memory activation mediated by norepinephrine (NE) [8].

Both HPA and ANS systems interact on multiple levels, involving NE and CORT as well as other mediators such as Nerve Growth Factor (NGF). Both systems can effect memory directly or indirectly as in the case of increased CORT levels reduces NGF during acute stress [9]. This NGF reduction can effect memory directly [10], or indirectly via NE level decrease (see below for the explanation of the effect). NGF is an important mediator of memory as well as a pivotal component of the current hypothesis and will be examined next.

Nerve Growth Factor (NGF) review

NGF is the best characterized member of the neurotrophin family, which is involved in a variety of signaling events, such as cell differentiation and survival, growth cessation, and apoptosis of neurons [11]. Stress, either acute [12] or chronic [9] can lead to NGF concentration increase. Further, increase in NGF concentration can affect memory directly [10] or indirectly by NGF being carried to the Stellate Ganglion via a retrograde transport [13] (Van Q). This increase in concentration has been shown to promote sympathetic sprouting [14], which in turn, leads to an increase in NE levels [15] Fig. 1. Brain infusion of NGF in mature rats leads to NE increase [15] with NE level increase enhancing memories of the traumatic event(s) [8]. NGF is not the only modulator of memory and development of PTSD in humans. HPA system via CORT also plays an important role in memory and development of PTSD.

The role of CORT in Post-Traumatic Stress Disorder development

Animal models have been used to quantify the role of CORT in mediating this biochemical pathway. Experiments utilizing the synthetic version of the steroid hormone cortisol (CORT) have shown a dose-dependent effect in which low-dose CORT enhances performance of memory-oriented tasks, whereas high-dose CORT impairs performance presumably by interfering with memory consolidation [4]. Finding that trauma victims who develop PTSD secrete lower levels of urinary CORT immediately after a trauma than victims who do not develop PTSD further support CORT role in PTSD [16]. Finally, the addition of supplementary CORT immediately following trauma leads to NGF reduction. [17] demonstrating

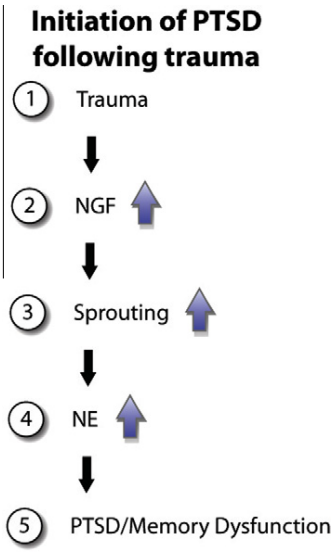

Fig. 1. Proposed mechanism for PTSD initiation with focus on NGF and memory.

the connection of NGF and CORT. Above evidence would suggest that early administration of CORT immediately after trauma would prevent PTSD development presumably due to interference with memory consolidation by direct effect of reduction of NGF, or indirect effect of NGF reducing NE, with either or both reducing memory consolidation and the like, Fig. 2.

Clinically evidence exists in the human model to support above view. A small randomized clinical trial was conducted by Israeli researchers [18] among 25 patients admitted to the ER following an automobile accident. In the trial, half of the patients were randomized to receive a single injection of hydrocortisone or saline placebo. The Israeli researchers found that the administration of CORT reduced the risk of developing PTSD by 60% [18]. Similar results were obtained when rats were exposed to the smell of a cat, early treatment with high-dose CORT reduced the prevalence of

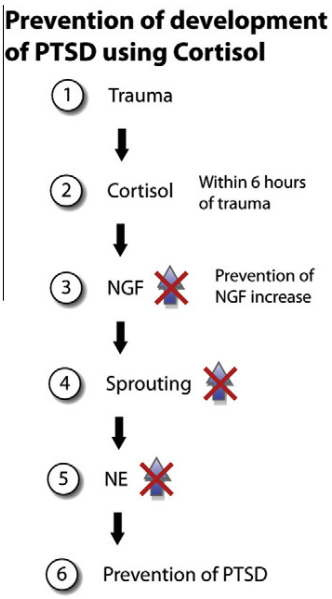

Fig. 2. Proposed mechanism for prevention of PTSD development by the use of cortisol.

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PTSD-like behavioral responses relative to saline-control treatment. Cue-induced freezing was significantly lower in the high-dose CORT-treated group [19].

HPA is one of two systems responsive to stress that is a focus of this publication as a modulator of memory and development of PTSD in humans. ANS system via NE also play an important role in memory effect of trauma as well as development and persistence of PTSD. Below is a review of effective treatment modality of PTSD using ANS modulation.

The evidence and background for use of Stellate Ganglion Block as a PTSD treatment

ANS and its interaction with NGF is summarized above. One of the integral parts of the sympathetic system is a cervical sympathetic ganglion, called Stellate Ganglion. Evidence exists that a local anesthetic blockade of the ganglion can successfully treat PTSD symptoms. This concept is not altogether novel, and research remains scant yet promising. Park et al. was among the first to report successful treatment of PTSD by a cervical sympathetic block in an animal model in 1997 [20]. In 2008, Lipov et al. documented reduction of PTSD symptoms following a Stellate Ganglion Block (SGB), an injection of local anesthetic next to the Stellate Ganglion [21]. The working hypothesis was that the autonomic nervous system modulates PTSD via a complex neurological pathway beginning with NGF and culminating in excess concentration of norepinephrine. This was described in Medical Hypothesis publication in 2009[22].

Results from subsequent confirmatory trials of the effectiveness of the SGB in reducing PTSD symptoms were published by Mulvaney [23], Lipov et al. (2011) [24], Hicky et al. (2012) [25] and Lipov et al. (2012) [26]. The specific pathways by which SGB using local anesthetic modulates NGF and NE are summarized next.

The cascade of NGF and NE increase that starts with trauma is summarized in the NGF review above. Reversal of this cascade can be achieved by the application of local anesthetic to the Stellate Ganglion, an action known to reduce NGF[27] Fig. 3. This NGF reduction leads to the death of the new nerve shoots [28] since persistence of sprouting requires constantly elevated NGF [28]. Furthermore, NE levels have been shown to be reduced by SGB as well [29].

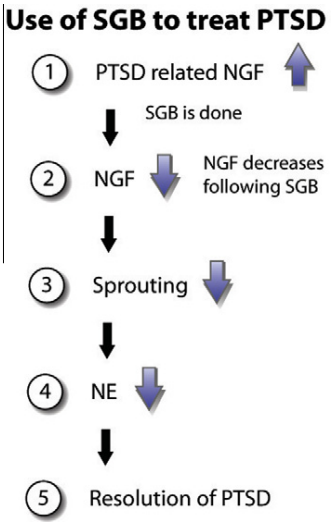

Fig. 3. Proposed mechanism for treatment of PTSD by the use of Stellate Ganglion Block (SGB).

Conclusion

We hope the evidence summarized here is both promising and compelling as the early steps in biological psychiatry. PTSD is a complex condition with a significant effect on the memory. Stress related memory dysfunction has been a focus of research for some time. Our hypothesis looks at the biology of PTSD-related memory dysfunction, as well as novel approaches becoming available as preventive and therapeutic modulation of this phenomenon. We believe that stress has a large impact on memory function, in large part due to NGF concentration increase and related changes in the cerebrum. The stress related NGF surge seems to be preventable by early administration of CORT. Further, chronically elevated NGF, and subsequent sympathetic sprouting leading to increased NE, can be reversed by the use of SGB. Both of the above interventions can affect PTSD related memory dysfunction in a positive way, suggesting the possibility of NGF as a "missing link" between memory consolidation and PTSD.

Our hypothesis provides a plausible explanation for early observations, specifically, the efficacy of an intramuscular steroid injection in preventing PTSD, as well as the Stellate Ganglion Block providing immediate and durable relief from PTSD symptoms. While previous publications have laid the groundwork for this hypothesis, additional research is required to further solidify our understanding of this mechanism and the populations for which it is most effective. Yet we believe this investment will yield significant returns in understanding of the underlying mechanisms of PTSD onset and maintenance. Most importantly, the clinicians may finally have more options to prevent and treat PTSD, perhaps introducing a new era in biological psychiatry.

Conflict of interest statement

None declared.

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