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Epigenetic alterations of BDNF DNA-methylation associated with Posttraumatic Stress Disorder: findings from the Korean Combat Veterans of the Vietnam War
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Abstract
Objective: Complex interactions between genes and environmental events may contribute to the development of post-traumatic stress disorder (PTSD). The aim of this study was to investigate whether epigenetic regulation of the brain-derived neurotrophic factor (BDNF) gene is a resilience marker of PTSD among veterans exposed to Vietnam War.

Methods: A total of 253 Korean combat veterans of the Vietnam War were included. The Clinician-Administered PTSD Scale (CAPS) and Combat Exposure Scale (CES) were assessed. BDNF DNA methylation levels at 4 CpG sites within the promoter region were quantified in the peripheral blood using pyrosequencing. The effects of BDNF methylation levels and clinical variables on the diagnosis of PTSD were tested using binary logistic regression analysis.

Results: Using the CAPS interview, combat veterans were grouped into those with (n = 127) and without (n = 126) PTSD. Subjects with PTSD showed a significant higher DNA methylation of 4 CpG sites at the BDNF promoter compared to those without PTSD. High BDNF methylation status at the 4th CpG site, high CES and alcohol use predicted significantly PTSD diagnosis.

Conclusions: The present study demonstrated an association between higher DNA methylation of the BDNF promoter region and PTSD. Our findings suggest that altered epigenetic programming of the BDNF gene is related to the pathophysiology of PTSD and stress resilience after trauma exposure.

PS256
New drug therapy and the effect mechanism that the central anticholinergic drug Trihexyphenidyl reduces flashback in PTSD. The second report
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Abstract
Objective: We developed the acetylcholine hypothesis to explain the cause of PTSD flashbacks; it states that PTSD flashbacks are caused by the hyperexcitability of the memory-related circuit of the acetylcholine (ACh) nervous system (ACH-MRC), comprising ACh1 (medial septal nucleus) and ACh2 (diagonal band of Broca) to hippocampus and ACh4 (Nucleus basalis of Meynert) to amygdala paths, i.e., by the abnormal secretion of ACh. Based on this hypothesis, we would like to report a new drug therapy using the central anticholinergic agent trihexyphenidyl (TP) and its action mechanism. At the 12th World Congress of Biological Psychiatry held in Athens (June 2015), we reported favorable results of a clinical trial of TP conducted in seven subjects. Since then, we administered TP to 16 subjects presenting with flashbacks (FB) and would like to report our findings.

Methods: We administered TP to 23 patients experiencing flashbacks. TP was mainly administered once at 2 mg in the form of draught when flashbacks occurred. The dose was adjusted according to severity; for a serious case, TP was administered thrice at 2mg/day for several weeks. However, no side effects have been reported.

Informed consent was obtained from all patients. This study was approved by the Ethical Committee of Warakukai.

Results: PTSD was diagnosed and evaluated using DSM-5, IES-R, and CAPS assessment. These evaluations showed an extremely beneficial effect. Twenty three cases were evaluated; 7 cases up to 2012 and 16 cases from 2012 to 2015. Of these, 65.2% (15/23) showed complete remission (CR), and 34.8% (8/23) showed partial remission (PR), indicating a favorable outcome. CR(65.2%)+PR(34.8%)-100%.

Conclusion: Thus far, no drug with definite effects on PTSD has been identified. Furthermore, the mechanism of action of drugs believed to have effects on PTSD is unclear. TP exhibited an excellent effect on PTSD flashbacks. The effect was rapid and could be seen in 1 to 1.5 hours after dosing, with the effect lasting for 5 to 6 hours. FB is an important, central symptom of PTSD, and improvements in FB lead to improvement of other PTSD symptoms. We primarily used single doses of the drug. For severe cases, we administered 3T (1T-2mg) once daily for 1 to 2 months, with close monitoring of side effects. Thus far, no patients have shown any side effects.

Disclosure: There are no financial conflicts of interest.

PS257
The effects of brain-derived neurotrophic factor (BDNF) micro-infusion on the impaired fear extinction of the animal model of PTSD.
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Abstract
Although the impaired extinction of fear memory (Ext) is one of the hallmark symptoms of posttraumatic stress disorder (PTSD), the underlying mechanisms of impaired Ext are unclear and effective pharmacological interventions have not yet been developed. Recently, the neuronal plasticity induced by brain-derived neurotrophic factor (BDNF) in infralimbic (IL) prefrontal cortex and/or hippocampus were shown to be crucial for the Ext of naive rats.

We used a single prolonged stress (SPS) paradigm, which mimic the pathophysiological abnormalities and behavioral characteristics of PTSD including the impaired Ext. The current study was conducted to investigate the expression of BDNF in the brain of SPS rats, as well as the therapeutic efficacy of intracranial BDNF micro-infusion for the impaired Ext of SPS. Either the sacrifice of rats for BDNF quantification or the micro-infusions for the behavioral study were conducted just before Ext training session (24hr after fear conditioning), and the micro-infusions were targeted to the IL, or Prelimbic (PL) prefrontal cortex, or ventral hippocampus (vHPC).

The mature BDNF protein expression of SPS rats were significantly reduced just before Ext training in both the medial prefrontal cortex and the hippocampus. In addition, the micro-infusion of BDNF into IL or into vHPC, but not into PL, induced the significant reduction of freezing behavior at the Ext training session and Ext test session (24hr after Ext training), and these effects were commonly seen in the naive rats and the SPS rats.

Our results indicates that the neuronal plasticity induced by BDNF in IL and vHPC are, at least in part, involved in the