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Potential application of the D-amino acid oxidase (DAAO) inhibitor sodium benzoate for individuals experiencing psychological stress after traumatic events

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Abstract

Preventing post-traumatic stress disorder (PTSD), which is harmful in terms of human resources and burdens society, is an urgent issue. The glutamatergic system, a newly-identified target site of recent pharmacological interventions for various mental disorders, could be a potential pathway. A recent study confirmed that sodium benzoate, which is a D-amino acid oxidase (DAAO) inhibitor that is used as a safe food additive, is therapeutically effective for certain mental disorders. Studies also indicated a medium effect size on the perceived stress and 28%-61% reduction of panic symptoms. Hereby, we propose a novel clinically oriented medical idea: "proper use of sodium benzoate in the preparation of rations for individuals with mental disorders who will be or are currently exposed to stressors could be a feasible method for preventing PTSD and other associated mental disorders". While this idea remains to be tested, its application could be helpful for rescue workers or victims of disaster.

Humans may experience traumatic events, such as accidents, natural disasters, and wars, during their lives. Acute and chronic exposure to great stress and trauma can result in acute stress disorders, which may progress to post-traumatic stress disorder (PTSD), which can be accompanied by psychotic symptoms, depression, anxiety, and poor sleep [1-3]. Patients suffering from PTSD may experience re-experiencing symptoms, avoidance of internal/external cues about the event, alterations in cognition and mood, and arousal symptoms (such as irritable behavior and hypervigilance) [4]. PTSD harms the patients, and the burden of these problems could be considerable, due to associated economic cost related to the health care, unemployment, and disability [5]. Effective treatment and prevention are needed. Since some traumatic events may affect large populations (such as natural disasters and wars), cost-effectiveness becomes an important consideration. A wide range of pharmacological preventive agents (β-blockers, hydrocortisone, selective serotonin reuptake inhibitors, oxytocin, gabapentin, fish oil, dexamethasone, tricyclic antidepressants and chloral hydrate) have been used to prevent this condition; however, the efficacy of these agents remains controversial [6,7]. Military personal may suffer from PTSD as well as other disorders related with nervous function, such as Gulf War illness (GWI), after operations involving traumatic experience. Recently, a study elucidated that altered immune response could be one of the pivotal mechanisms [8]. Providing prevention for this problem via inhibition of the inflammatory response, with low cost-effectiveness ratio, is an urgent topic.

The biological mechanisms of PTSD are complex and unclear. Recently, the role of altered glutamatergic activity in PTSD has been revealed [9-11]. This evidence implies that glutamatergic agents could be a future pathway for intervention in PTSD [9]. Notably, glutamatergic treatment has also been proposed for depression, anxiety, and psychosis [12,13]. Several glutamatergic modulators [14], including N-methyl-D-aspartate (NMDA) receptor agonists; glycine, D-serine and L-serine; and glycine transporter inhibitors, could be feasible agents for treating psychiatric disorders. In particular, we note that sodium benzoate, which is a D-amino acid oxidase (DAAO) inhibitor [15] and could be used as a safe food additive [14], may be an alternative option to prevent mental disorders in people exposed to stress via rations used for emergency purposes.

Sodium benzoate enhances NMDA receptor activation though DAAO inhibition. DAAO inhibitors prevent the degradation of D-amino acids, including D-serine, by inhibiting the DAAO enzyme. D-serine is a potent co-agonist of NMDA receptors. Studies have shown that D-serine through NMDA receptors activation, enhance extinction of fear memories which are associated with PTSD [16]. Modulating D-amino acid concentrations through DAAO inhibition has far-reaching implications for various physiological functions, encompassing hormone secretion, synaptic transmission, and cognition. This effect on NMDAR activation is also important for enhancing synaptic plasticity. A recent animal study demonstrated that the synaptic plasticity could be related to resilience against stress [17]. Recently, the role of altered glutamatergic activity in PTSD has been revealed, suggesting that glutamatergic agents could be a future pathway for intervention in PTSD [9]. Studies on the glutamate-based treatment for PTSD were summarized [18]. It has been confirmed that due to efficacy of sodium benzoate, it can be applied for the treatment of several mental disorders, such as early psychosis [19].

Along with its glutamatergic mechanism a recent study of Brahmarchari et al. indicated that sodium benzoate might inhibit the inflammatory responses, including the inducible NO synthase and cytokines, in the mouse microglia and primary human astroglia cell [20]. This process could serve as a therapeutic mechanism for treating PTSD and in a wide range of neuropsychiatric disorders.

Here we propose a feasible idea for prevention: "Proper use of sodium benzoate in the preparation of rations for personnel who will be or are currently exposed to stress could be a feasible method of preventing PTSD and other associated mental disorders". This approach could be implemented in the preparation of compact military or emergency food rations. Additionally, compact rations (i.e., BP-5, Humanitarian Daily Rations) are often employed in disaster relief. It is clear that PTSD and related mental illnesses are prevalent after disasters. A similar idea could be applied for victims of disaster.

To the best of our knowledge, no study has tested this idea to date; however, several studies have confirmed the efficacy of sodium benzoate (at doses ranging from 250 mg to 2000 mg per day) in treating mental disorders [15,19,21]. Notably, a recent study showed that sodium benzoate reduces perceived stress among depressed elderly individuals [22] and relieves symptoms of panic disorder [23]. This evidence supports the present hypothesis. We calculated the effect size for perceived stress reduction [22] (sodium benzoate: Cohen' d = 0.42; placebo: Cohen'd = 0.11), and the percentage of relieves symptoms in panic disorder [23] (28% reduction at week 2, and 61% at week 6) according to the published data. These statistics may imply that sodium benzoate could produce a certain effect size. However, double-blind, randomized prospective clinical trials are needed to confirm this hypothesis [24]. Additionally, studies with

animal models [25] could directly test this hypothesis and the underlying mechanism. We speculate that the DAAO inhibitors can help prevent the PTSD, as DAAO inhibitors may alter the glutamate system, which plays a role in the characteristics of PTSD, such as depression, anxiety, and psychosis, and also the resilience that related with stress response [26,27]. As the optimal dosage for prevention is not yet clear, it should be noted that the permissible limit of consumption of this food additive is 0–5 mg/kg of body weight [14]. However, there are two limitations: (a) The optimal dosage and duration of treatment are unclear; (b) The effect size is unknown.

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Author Contributions

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Li-Chung Huang: conceptualization, writing - review & editing

Yen Kuang Yang: writing - review & editing, supervision

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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