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Time course of zinc deprivation-induced alterations of mice behavior in the forced swim test

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Abstract:
Background: Zinc is an important trace element essential for numerous bodily functions. It is believed that a deficiency of zinc can lead to various conditions, including depression, on which this study is focused. It is still not known if hypozincemia leads to the development of depression or whether zinc deficiency is a result of depression. It is hypothesized that zinc may be a therapeutic agent or supplement that would help to reverse the symptoms of this disease.
Methods: In the present study, the behavior of mice was assessed 2, 4, and 10 weeks following administration of a zinc deficient diet. To evaluate animal activity we used the forced swim test (FST).
Results: After 2-week zinc deprivation we demonstrated a significant reduction in the immobility time. However, after 4 and 10 weeks of zinc deprivation the mice exhibited an increased immobility time. There were no changes in locomotor activity at each time period. After 2-, 4- and 10-week zinc deprivation and the subsequent FST, serum zinc concentration was decreased and determined to be 59, 61 and 20%, respectively, compared with appropriate controls. The serum corticosterone concentration in mice after 2-, 4- and 10-week zinc deprivation and subjected to the FST was also assessed, whereby the differences between the control and experimental animals were demonstrated (increased by: 11, 97 and 225%, respectively).
Conclusions: The obtained results indicate that zinc deprivation induced "pro-depressive" behavior (after the initial period of "anti-depressive" behavior). This pro-depressive behavior correlates with enhanced serum corticosterone concentration.

Key words:
zinc deficiency, serum concentration, zinc, corticosterone, HPA axis, depression, FST

Introduction

Considered to be one of the most common psychopathological disorders, depression can affect one in six men and one in four women, with varying degrees of severity and recurrence [11]. It is a poorly understood mental condition characterized by low self esteem, immune system malfunction [18], anorexia and low motivation, along with social implications [3].

It is believed that the metal element zinc plays a role in this disorder [40, 47, 52]. Zinc is an important element which is essential for numerous bodily processes, including brain function, DNA replication and protein synthesis; more than 300 proteins are known to require zinc [18, 48].

Zinc homeostasis is maintained strictly by the blood-brain barrier and blood-cerebrospinal barrier. It is hypothesized that proteins requiring zinc for function are responsive to changes in dietary zinc; decreased levels of zinc have been observed in extracellular [47] but not in whole hippocampal tissue during zinc deficiency. An alteration in zinc homeostasis can result in clinical depression, changes in behavior and mental function. A reduced blood zinc level is observed in major depression and is proposed as a state marker of depression [16, 33]. Zinc is thought to be an inhibitor at the NMDA receptor, which itself may be involved in the psychopathology and therefore a target for the treatment of depression [8, 25, 40]. The relationship between neuronal function and behavior is vital to the understanding of the dynamics of complex mental disorders such as depression and anxiety. Previous studies have indicated that zinc plays a role in anxiolytic and antidepressant therapy; this has been demonstrated in preclinical tests including the elevated plus maze test and four-plates test [28], forced swim test (FST) [12, 13, 24, 30] and tail suspension test (TST) [8, 30].

Up to 50% of the population is thought to have inadequate levels of zinc in their blood in both developed and underdeveloped countries worldwide and may be a possible reason for some symptoms of depression [2]. Zinc enhances the antidepressant-like effects of conventional antidepressants (including imipramine) in the FST, TST and chronic unpredictable stress (CUS) model [5, 8, 39, 41]. Of great concern are recent findings coming from clinical studies in which zinc supplementation enhances the efficacy of antidepressant therapy, particularly in treatment resistant patients [22, 32].

It has been suggested that the stress is related to an increase in glucocorticoid concentration [38, 47, 52]. The hypothalamus-pituitary-adrenal (HPA) system is the final common pathway in the mediation of the stress response [1]. It is thought that zinc deficiency can cause alterations of the HPA axis in depression. The hypothalamic overproduction of the corticotropin-releasing hormone overstimulating adrenocorticotropin in the anterior lobe of the pituitary [56] results in excess production of the glucocorticoid corticosterone in rodents. This dysregulation seems to be an important factor in the pathogenesis of depression [42, 45, 47, 51].

The aim of this study was to determine whether administration of a diet deficient in zinc would cause "depressive behavior" and if such behavioral alterations would correlate with serum corticosterone and zinc concentration. The FST was used to assess the behavioral changes ("depressive state") of the animals during zinc deficiency over a period of 2, 4 and 10 weeks.

Materials and Methods

Animals

Male CD-1 mice (3 weeks old) were housed under the standard laboratory conditions with a natural day-night cycle, a temperature of 22 ± 2°C and the humidity at 55 ± 5% as well as access to food and water *ad libitum*. Each experimental group consisted of 7–8 animals. All of the procedures were conducted according to the National Institute of Health Animal Care and Use Committee guidelines, which were approved by the Ethical Committee of the Jagiellonian University Medical College, Kraków.

Zinc deficient diet

Control (33.5 mg Zn/kg) and zinc deficient (0.2 mg Zn/kg) diets were purchased from MP Biomedicals (France). Mice were assigned to one of six different groups according to the diet and duration of the diet administration (Fig. 1).