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Review article

Essential elements in depression and anxiety. Part I

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ABSTRACT

Essential elements are very important for the proper functioning of the human body. They are required for fundamental life processes such as cell division and differentiation and protein synthesis. Thus a deficiency of these essential elements is associated with an enormous health risk that can ultimately lead to death. In recent years, studies have provided valuable information on the involvement of essential elements in psychiatric disorders, in particular depression and anxiety.

There is strong evidence indicating that deficiency of essential elements can lead to the development of depressive and/or anxiogenic behaviour and supplementation can enhance therapeutic effect of antidepressants and anxiolytics. This review presents the most important results from preclinical and clinical studies showing involvement of essential elements such as zinc, magnesium, lithium, iron, calcium and chromium in depression and anxiety. From these studies it is evident that different types of depression and anxiety respond to treatment at different receptors indicating that the underlying mechanisms are slightly different. Furthermore, administration of low dose antidepressants supplemented with an element is effective and can reduce unwanted side effects in different types of depression/anxiety.

Contents

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Introduction

Essential elements are required for the proper functioning of living organisms (e.g. [1]) and are classed as essential if they are required for a specific biochemical function, or if dietary deprivation in animal experiments causes defects in biological function, which can be restored or prevented by administration of the element. These elements are involved in a diversity of mechanisms such as (i) regulation of cellular function, (ii) growth and maintenance, (iii) neuromodulation, and are either synthesised by the body or obtained through diet. A lack of essential elements may result in severe consequences including alterations in immune function, altered cognition and growth and developmental changes [1].

Data from preclinical and clinical studies have shown the importance of many elements in the pathophysiology of affective disorders [2–7]. There is an abundance of evidence regarding the involvement of elements in depression and anxiety, particularly alterations of metal element homeostasis, however the results have been slightly conflicting. Many elements have an influence on the neural transmission involved in emotional processes, such as the serotonergic, noradrenergic, dopaminergic, glutamatergic and GABAergic systems [8–11].

Deficiency of essential elements can arise through low dietary intake. A Western-style diet high in processed foods (including processed meat, white bread, sugar) is associated with a higher incidence of affective disorders compared to a traditional diet (including fruit, vegetables, wholegrain foods) [12]. Based on preclinical studies, deficiency of elements can lead to neurodegenerative processes and, by association, learning and memory impairments [13]. Patients suffering from depression and/or anxiety also show disturbances of cognition [14,15]. Reversing the deficit of the essential element concerned improves memory function [16]. Supplementation with the deficient element improves the therapeutic effect of commonly used antidepressants, and enhances antidepressant therapy in refractory depression [17]. In addition, supplements of essential nutrients have been shown to be beneficial in susceptible patients, and furthermore, amino acid supplements, such as tryptophan, are also effective as they can be converted into neurotransmitters [18]. Some elements may have similar functions (i.e. iron and manganese) and could compensate for a deficiency of another element [1].

This review will analyse preclinical and clinical evidence regarding essential elements and their relationship with the pathophysiology and treatment of depression and anxiety. We will discuss the most important data from preclinical and clinical studies indicating involvement of essential elements including zinc, magnesium, lithium, iron, calcium and chromium in depression and anxiety.

Zinc

Zinc is widely recognised as one of the most common trace elements involved in the pathophysiology of depression and anxiety. Zinc is essential for numerous bodily functions, including replication, transcription and protein synthesis, and can thus influence cell division and differentiation [32]. According to the Institute of Medicine of the National Academies the daily requirement for zinc varies depending on age and gender [33]. Adequate daily zinc allowance is 3–8 mg for children, increasing for teenagers and adults to 11 mg (for males) and 8–9 mg (for females). During pregnancy and lactation zinc requirements increase to 11–13 mg. The main sources of zinc include red meat, seafood (in particular oysters which contain 493% of the daily recommended allowance), nuts, beans and whole grains [33].

Zinc deficiency

Early clinical studies reported lower zinc serum in depressed patients compared to healthy patients [4,34,35] and later was proposed as a state marker of depressive disorder [17,34,36]. Thus numerous studies have sought to determine whether low zinc levels contribute to the development of depressive symptoms, or whether low zinc levels are a consequence of the mechanisms that lead to depression. Behavioural paradigms such as the forced swim test and tail suspension test are used in pre-clinical studies to determine the cause of depression and to screen for potential antidepressant treatments.

Animals fed a zinc deficient diet exhibited increased immobility time in FST [2,37–41] or TST [42], indicating that zinc deficiency contributes to the development of depressive-like behaviour. Moreover, zinc deficiency impaired the efficacy of numerous antidepressants which have different mechanisms of action [2,39,41,42].

Together these results indicate that zinc deficiency plays an important role in the development of depression, and the subsequent restoration of zinc reverses behavioural signs of depression in animal models.

Antidepressant effects of zinc

Subsequently the antidepressant effects of zinc were investigated in pre-clinical and clinical studies – zinc was active in the screening tests and models of depression indicating the antidepressant properties of zinc (Table 1 describes commonly used animal tests and models of depression). Different zinc salts such as zinc sulphate, zinc hydroaspartate or zinc chloride showed antidepressant properties in the forced swim test (FST) [7,43–46], tail suspension test (TST) [46,47], chronic mild stress (CMS) [48], chronic unpredictable stress [49] and olfactory bulbectomy (OB) [7] models of depression. Moreover, joint administration of zinc and antidepressants (both ineffective doses) with diverse mechanisms of action was active in the FST [44,45,50,51], TST [47] and CMS [49]. This suggests that zinc may enhance antidepressant action and reduce side effects of commonly used antidepressants. Zinc supplementation seems also to reduce the time required to achieve a therapeutic effect.

These findings were repeated in clinical studies. In 1997, Maes and colleagues demonstrated that serum zinc levels were significantly lower in treatment resistant depression (TRD) patients than in healthy patients [34]. Siwek et al. [17] showed that the serum zinc concentration in treatment resistant patients was 14% lower compared to controls. In this study, 60 patients fulfilling criteria for major depression received imipramine