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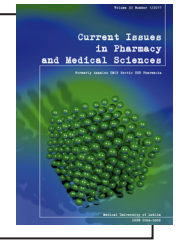

Selenium and manganese in depression – preclinical and clinical studies

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ABSTRACT

According to the World Health Organization estimates, approximately 10% of the world's population is affected by depressive disorders. Furthermore, even in high-income countries, many people with depression are not treated, which can lead to serious health consequences and a global economic loss. Unfortunately, the current pharmacotherapy of depressive disorders is characterized by unsatisfactory efficacy and the therapeutic effect is accompanied by many side effects. For this reason, there is still ongoing worldwide research to find new antidepressant therapies. In recent years, many data have been shown that essential elements demonstrate the antidepressant action and increase the effect of antidepressants. In this paper we present the results from the preclinical and clinical studies published over the years which show the involvement of selenium and manganese in depressive disorders. In this article, the relationship between the amount of these microelements in a diet and depression is reviewed and what's more, the association among these elements in different biomaterial and their relations to depressive symptoms is presented. Additionally, we discuss the possible influence of selenium and manganese on modulating neurotransmitter system involved in depression.

INTRODUCTION

Depression is currently regarded as the disease of the XXI century civilization. World Health Organization (WHO) data indicate that depressive disorders currently affect around 350 million people worldwide. It is common among young people – according to the WHO estimates, 4-8% of all teenagers manifest symptoms of depression [58]. The data concerning Polish youth are disturbing because the proportion of sufferers ranges from 27 to 54% [32]. Depression is characterized by severe mood disorders persisting for an extended period of time and resistant to the influence of external events. People with depressive disorders feel deep sadness, they have reduced activity and show loss of self-confidence and low self-esteem. Moreover, they experience problems with memory and concentration, as well as sleep and appetite disorders. Usually the symptoms of depression prevent the patient from functioning normally, bring about serious social and family problems, and, most importantly, result in ill health. Furthermore, the increasing number of suicides is a serious issue. More than 800 000 people die annually because of suicide, which is the second leading cause of death among people in the age group of 15-29 years [58].

For more than 50 years, the pharmacotherapy of depressive disorders has been using drugs which increase the level of catecholamines in the central nervous system. Unfortunately, their efficiency is approximately 60-70%. They also have many side effects and require from two to four weeks to obtain the therapeutic effect [46]. Therefore, there is still ongoing worldwide research to find new and safer antidepressant therapies.

Recently, a number of preclinical and clinical studies have been accumulated which indicate the antidepressant activity of essential elements and their positive effects in the prevention and treatment of depression. The acquired data have shown that taking-in essential dietary supplements decreases the extent and frequency of symptoms in patients with mental disorders [23,31]. Diet is also likely to have an influence on genetic, hormonal, immunological, biochemical and neurodegenerative factors involved in depression [25,36]. Because of their content in the body and the value of their daily requirement, essential elements are divided into macronutrient and trace elements. For macronutrients, including

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calcium, phosphorus, magnesium, sodium, potassium, chlorine and sulphur, a daily need of over 100 mg is required, while their content in the organism is higher than 0.01%. Trace elements are found in the body in an amount of less than 0.01%, and their daily demand is below 100 mg. Such micro elements include iron, copper, zinc, boron, manganese, molybdenum, iodine, fluorine, selenium [60].

In recent years, some evidence has emerged regarding the involvement of essential elements in depression, particularly, the role of selenium and manganese. The aim of this paper is to review the preclinical and clinical studies published over the years which examine the role of these micro-elements in depressive disorders. The intent is to ascertain whether changes in the levels of selenium and manganese are responsible for antidepressant-like effects or depression-like behaviour.

SELENIUM

A daily selenium intake of less than 0.1 mg/kg of body weight may cause a deficiency of this biometal in the body, while the consumption of more than 1 mg/kg of body weight may bring about adverse effects, such as a garlic smell from the mouth, hair loss, decolorization of the nail plate, diarrhea and neurological disorders. Selenium deficiency is diagnosed in humans when the level of this element is equal to or less than 85 µg/l [21]. The daily intake of selenium by adults varies in different countries. This may be caused by e.g. various eating habits (Fig. 1) [10,11,29,34,41,55,57]. A study evaluating the level of selenium in residents of Central Poland has determined that the daily consumption of this biometal was approx. 30-40 µg [57]. The latest literature data indicate the suitability of selenium in the prevention and treatment of depressive disorders, as demonstrated in both preclinical and clinical trials.

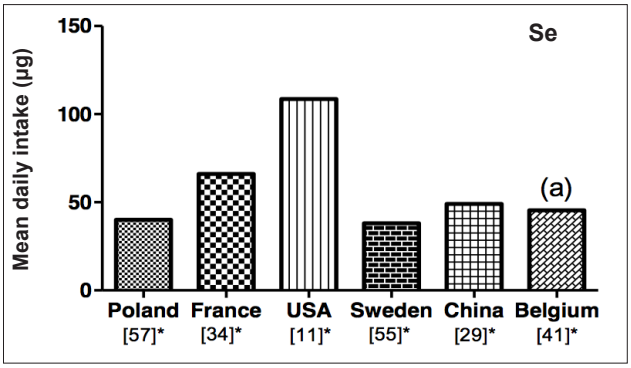

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Figure 1. The mean daily dietary intake of Se by adults in different countries (a-average of interval)

Preclinical studies

The antidepressant effect of organic selenium compounds was demonstrated in tests of depression in animals. Such tests included the forced swim test (FST) [18, 48, 56] and tail suspension test (TST) [13,18,56]. In such work, the pretreatment of mice with dopamine D_1, D_2 and D_3 receptor antagonists (haloperidol, SCH23390 (R-(þ)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phe- nyl-1H-3-benzazepine-7-ol) and sulpiride) prevented the anti-immobility effect of methyl phenyl selenide in the FST [47]. These results suggest that the dopaminergic system may be involved in the antidepressant-like action of this selenium-containing molecule. In contrast, the antidepressant action of bis selenide in the mouse TST was blocked by an inhibitor of serotonin (5-HT) synthesis (p-chlorophenylalanine methyl ester, PCPA), a $5\text{-HT}_{2A/2C}$ receptor antagonist (ketanserin), and a 5-HT_3 receptor antagonist (ondasentron) [26]. Moreover, the antidepressant-like effect of a selenium compound called ebselen [2-phenyl-1,2-benzisoselenazol-3(2H)-one] was not reversed by PCPA, ketanserin and 1-(2-methoxyphenyl)-4[-(2-phthalimido)butyl]piperazine) (NAN-190, a 5-HT_{1A} receptor antagonist) in the FST in mice [39]. According to these data, the participation of the serotonergic system in the antidepressant activity of selenium is not clear, and needs further investigation. Interestingly, bis selenide at a subeffective dose increased the effect of inactive doses of fluoxetine in the TST, which was manifested by a statistically significant reduction in the time of animal immobility [26].

As regards the role of the noradrenergic system on the antidepressant-like action of (octylseleno)-xylofuranoside (OSX), it was shown that pretreatment with an α_1-adrenoceptor antagonist and an α_2-adrenoceptor antagonist reversed the anti-immobility effect of OSX in the TST in mice [38]. In addition, the same results were obtained with naloxone (a non-selective antagonist of opioid receptors) in the FST, which also demonstrated the possible contribution of the opioid system in the antidepressant activity of m-trifluoromethyl-diphenyl diselenide [9].

Clinical studies

The benefits of selenium supplementation have been demonstrated in young people abusing alcohol, particularly in those with coexisting depression. Alcohol abuse may in fact lead to selenium deficiency, and the overlapping of these two factors (alcohol and low selenium levels) may result in the development of depression and suicidal behaviour in adolescents [49, 50]. It was also demonstrated that consuming 100 micrograms of selenium a day brought about significant improvement in the clearheaded/confused, elated/depressed, composed/anxious, and confident/unsure sub-scores [14]. In addition, mood changes were seen to correlate with the level of selenium in the diet, and a 5-week supplementation regressed the observed disorders [6]. In a study of selenium intake, it was found that selenium in the diet is associated with the Beck Depression Inventory [BDI] score, and the total energy-adjusted intake of selenium could play a significant role as a factor of risk of moderate depression [5]. Moreover, research conducted on participants aged 65 and over from two provinces in China revealed that higher levels of selenium measured in nail samples correlated with lower Geriatric Depression Scale scores [17].

Gosney *et al*. [20] observed that an 8-week course of selenium supplementation significantly improved mood in both residential and nursing home residents. This effect was allied with increased concentration of selenium in the serum. In contrast to these data, a randomized trial showed that after a 6-month selenium treatment, the mood or quality of life was not enhanced in volunteers aged 60-74, although the plasma selenium status was higher than before the research [40].

These differences may be associated with the selenium baseline concentration (mean values: 92 µg/L and 81 µg/L, respectively) or/and selenoenzyme activity in the studied subjects.

It is worth noting that supplementation with selenium in the prenatal period reduced the risk of postpartum depression [33]. In addition, low levels of selenium in the diet increased the risk of subsequent relapses in women with a history of a severe depressive episode [35]. Thus, it is believed that, in the future, selenium may be used as a marker of the risk of depression, which in turn will allow for the early treatment of this disease.

Still, it must be noted that at the 12-month evaluation of selenium therapy in HIV-positive drug abusers, mean BDI scores were slightly lower (by 9%) in the selenium-receiving participants, when compared to the measurements determined at the baseline visit and that of a placebo-treated group (13%) who were without influence of current drug use, antiretroviral treatment or viral load [52].

It is also important to point out that a Multi-country project on the role of Diet, Food-related behaviour and Obesity in the prevention of Depression (MooDFood) is going to be conducted. This will examine different nutritional and lifestyle strategies (multi-nutrient supplement and food-related behavioural change) that might promote mood and health improvement in high-risk, overweight European Union citizens [43]. For instance, the role of dietary selenium will be studied in patients who have elevated depressive symptoms, but who are not currently meeting the criteria for an episode of major depressive disorder or who have not met them in the last 6 months. The study was registered in August 2015 and is ongoing.

MANGANESE

According to the Food and Nutrition Board of the National Academy of Sciences, an Adequate Intake of manganese is 1.8 mg per day for women > 19 years old and 2.3 mg per day for men > 19 years old [24]. The daily food intake of manganese by adults is at a level of from 2.2 mg to 5.9 mg in different countries (Fig. 2) [3,4,12,19,27,28,34, 42,44]. It has been reported that the daily dietary intake of manganese by women below 1 mg causes altered mood in women during the premenstrual phase of their estrous cycle [37]. Manganese is neurotoxic at higher exposures, but it has been estimated that only 1-5% of ingested this biometal is absorbed in adults [2]. Manganese is considered an essential and critical nutrient, and its deficiency or overabundance may cause depressive disorders. Recently, many studies have been conducted indicating the role of manganese in depressive disorders, but its impact on depression is still unclear. The findings of research suggest that deficiency or overabundance of manganese may cause depressive disorders.

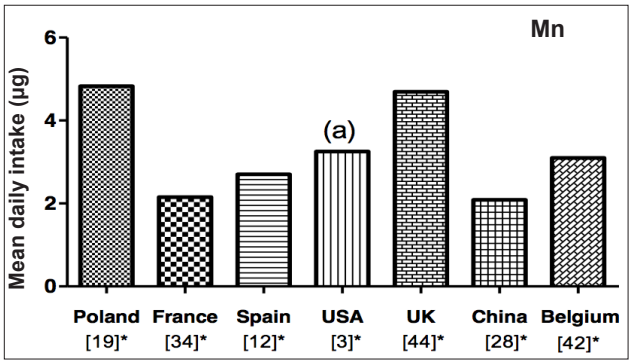

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Figure 2. The mean daily dietary intake of Mn by adults in different countries (a-average of interval)

Preclinical studies

According to the most recent data, manganese exposure has altered the behavior of animals in tests of depression [59]. The authors therein found that the immobility time in female and male rats treated with manganese at 1 and 5 mg/kg for thirty days was increased from that of control animals in the FST. Moreover, the assessment of tissue level of this biometal in the striatum of manganese exposed rats showed that the accumulation of manganese was not gender-dependent, but there was noticeably statistically significant dose-dependency. Interestingly, a 5-week course of manganese treatment (10 mg/kg) demonstrated that, compared to controls, the tissue content of dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC, a metabolite of dopamine) was significantly increased in the striatum, but the course of treatment had no influence on the content level of homovanillic acid (HVA, a metabolite of dopamine) or 5-HT and 5-hydroxyindoleacetic acid (5-HIAA, a metabolite of 5-HT) [7]. However, the tissue level of norepinephrine measured in the frontal cortex was decreased in manganese-intoxicated rats. This effect seems to be allied with the lokomotor deficits induced by manganese within these animals. With regard to the notion that interaction of manganese with the noradrenergic system leads to the emergence of depressive disorders, it requires further research. What is interesting, the immobility time in the FST was higher in the manganese-treated rats in this study.

In spite of evidence of a manganese interaction with the neurotransmission of the dopaminergic system, it has been reported that the striatal concentration of monoamines and their metabolites was dependent on the route of manganese administration [30]. Indeed, manganese in the drinking water did not affect the content of dopamine, DOPAC and HVA in this structure of the mouse brain after 8 weeks of treatment. Additionally, the results showed that there was no difference in the 5-HT level between the animals exposed to manganese (in this manner) and the control group, but an increase of 5-HIAA was observed. However, the immobility time was increased in the manganese-treated animal in the FST. These findings suggest that this biometal may induce depressive-like behaviours through an association with the dopaminergic and serotonergic neurotransmission systems. Explanation of this link, however, requires further research.

Clinical studies

The most recent data indicate a manganese involvement in human depressive disorders. Taking this into account, the relationship between nutrient intake and depressive symptoms was explored in Spanish children aged 6-9 years [45]. Using the Center for Epidemiological Studies Depression Scale for Children Questionnaire, depression symptoms in schoolchildren after a three-day assessment of the diet

were evaluated. In this study, the intake of manganese was lower in the participants with depressive symptoms than in the group with non-depressive symptoms.

Apart from this, Abdalian *et al*. [1] investigated patients who were on long-term parenteral nutrition including manganese supplementation. The researchers observed that these patients reported various mental disorders, e.g. depression (66%), during this study. Interestingly, the concentrations of metals, such as manganese, were examined in the urine of American adults aged 20-80 years who suffered from depression [51]. In this research, the results demonstrated that the level of urinary manganese was higher in the cohort with depression. In contrast, Fukushima *et al*. [16] showed that the whole-blood manganese measured in Parkinson's disease (PD) patients without depressive symptoms was higher than in both the PD patients with depression and the control group. Moreover, in a further study by these researchers, it was observed that the blood concentrations of manganese and zinc in the PD patients with depression and the controls were correlated with each other, but this was not so in the PD patients without depressive symptoms [15]. Due to these differences in the level of manganese, the authors suggest that in non-depressive PD patients, an additional route of enhanced manganese intake could exist.

Beyond the aforementioned, Hong *et al*. [22] showed that the adverse impact of manganese exposure may contribute to the occurrence of co-morbid depressive disorders in children with ADHD. What is interesting is that depression symptoms measured using the Beck Depression Inventories-II were noticed in welders (53.5%) who were exposed to manganese-containing welding fumes during work on the San Francisco-Oakland Bay Bridge [8]. Furthermore, lately, attention has been paid to the role of antioxidant enzymes such as the manganese superoxide dismutase (MnSOD) activated by Mn^{2+} ion in depression. For instance, a Polish study reported that the enzyme activity of MnSOD was more decreased in patients with recurrent depressive disorders than that in a group of healthy subjects [53]. Nevertheless, no significant interrelation in the expression of this enzyme was found in both groups with the first episode of depression and with recurrent depressive disorders [54].

CONCLUSION

To conclude, conscious and reasonable supplementation of selenium and manganese may contribute to safer and more effective treatment of depressive disorders. In the treatment of patients with depression, attention should be paid to the proper selection of nutritional products to ensure the optimal supply of trace elements. Due to the antidepressant-like or the depression-like behaviour of microelements, we should consider taking multicomponent preparations. Therefore, more studies are needed to gain knowledge concerning the relationship between nutritional intake and depressive symptoms.

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