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Review article

Essential elements in depression and anxiety. Part II



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ABSTRACT

In this paper we continue to discuss the involvement of essential elements in depression and anxiety, and the possible mechanisms that link elements to the neurobiology underlying depression/anxiety. The present paper is focused on copper, selenium, manganese, iodine and vanadium. Different aspects of relationship between elements and depression or anxiety are reviewed, e.g. the association of the amount of an element in a diet or the serum level of an element and depressive or anxiety-like symptoms. Moreover, the relation of selected elements to the pathophysiology of depression or anxiety is discussed in the context of enzymes which require these elements as co-factors and are involved in the underlying pathophysiology of these disorders.

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Introduction

This paper provides an overview of the preclinical and clinical data concerning the role of essential elements in depression and/or anxiety, and the possible mechanisms that may mediate their involvement.

Several lines of evidence, both preclinical and clinical, indicates a potential link between essential elements and mental disorders: (a) there is an association of the amount of a nutrient in a diet and depressive or anxiety symptoms, (b) there is an association of serum level of an element and depressive or anxiety symptoms, (c) elements exert antidepressant or anxiolytic effects in preclinical tests of depression and anxiety, respectively, (d) supplementation of antidepressant or anxiolytic therapy with an element can improve the treatment outcome in patients. In Part I we discussed these aspects of relationship between essential elements and

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depression or anxiety with regards to zinc, magnesium, lithium, iron, calcium and chromium [1], whilst Part II is focused on copper, selenium, manganese, iodine and vanadium.

Furthermore, in the present paper a connection between selected elements and hypotheses concerning the neurobiology of psychiatric disorders is discussed. Enzymes that are involved in the synthesis and metabolism of neurotransmitters (such as serotonin, noradrenaline, dopamine) implicated in the pathophysiology and treatment of affective disorders or anxiety disorders may require metal elements as cofactors (e.g. enzymes involved in the synthesis and metabolism of catecholamines, including dopamine and noradrenaline, require copper as a cofactor). There is also a link between elements and a more recent hypothesis regarding the role of oxidative stress in affective disorders [2–4] or anxiety disorders [5]. Three forms of superoxide dismutases (SOD), an important antioxidant defence, are cofactored with copper and zinc (SOD 1 and 3) or manganese (SOD 2) [6]. Most studies have shown increased SOD activity in depression, however contradictory results have also been reported [3,7]. Another antioxidant enzyme, glutathione peroxidase (GPx), is cofactored by selenium [8], and decreased activity of GPx has been observed in blood of depressed patients [3,7].

Mustak et al. [9] analyzed eleven trace elements (Na, K, S, Ca, Mg, P, Cu, Fe, Zn, Mn and Al) in three types of bipolar disorder (I, II and V). The results demonstrated, among others, decreased Zn and Fe concentrations and increased Cu and Al levels in all types of bipolar groups when compared to controls. The results suggest that there is a definite imbalance in trace element homeostasis, for which the authors perceive the primary cause is increased Al concentrations [9]. Nevertheless, trace elements constitute an important either causative or therapeutic factors in neuropsychiatric disorders and their inter-relationships certainly need further examination.

Here, we discuss copper, selenium, manganese, iodine and vanadium relation to the pathophysiology of depression in the context of antioxidant enzymes, which alterations have been observed in depression and require these elements as cofactors.

Copper

The essentiality of copper for living organisms was first recognized nearly a century ago [10]. It has since been established that copper has a crucial role in erythropoiesis, myelin formation, synthesis of hormones, antioxidant protection and immune system modulation. Serving as a structural component and cofactor for many proteins and enzymes, copper regulates a large number of bodily biochemical processes, including cholesterol and glucose metabolism [11,12]. Therefore, tissues of greatest metabolic

activity such as liver, heart or brain are among the most copper-rich organs. The human body contains slightly >100 mg of this micronutrient. The Recommended Dietary Allowance (RDA) for adult men and women is 0.9 mg/day, increasing during pregnancy and lactation to 1–1.3 mg/day [12–14] (dietary allowances for each element is present in Table 1).

Copper homeostasis is of great importance to human health and guarantees proper utilization of other dietary elements, especially iron. Copper deficiency affects connective tissue leading to vascular and skeletal problems, causes neuronal degeneration, anemia, and cardiac and immune dysfunctions. Excess amounts of copper may result in cellular instability and damage due to the oxidative potential of the free metal [13,15]. Nevertheless, copper toxicity is rather rare in humans since copper almost always exists bound to proteins in biological systems. Copper loading is observed in disorders in which its biliary excretion is impaired, such as biliary cirrhosis and biliary atresia or in Wilson's disease (WD). Wilson's disease occurs due to a genetic disorder that leads to copper accumulation, particularly in liver, brain, kidney and cornea. Clinical manifestations of WD include liver damage, psychiatric symptoms, kidney and corneal abnormalities, arthritis and cardiomyopathy [13,15,16]. Patients with Wilson's disease often suffer from depression, anxiety and psychosis [16], and there is a case of a patient with WD with late onset, in which major depression was the first and the only clinical manifestation of the disease [17]. Moreover, serum copper has been suggested as a trait marker of unipolar depression [18]. The question then arises, what role does copper play in the course of affective disorders?

As a component of enzymes such as monoamine oxidase (MAO), dopamine β -hydroxylase (DBH) and tyrosine hydroxylase, copper has a pronounced influence on the catecholaminergic pathways (Fig. 1) involved in the pathophysiology of depression [12,19]. Dietary and genetic copper deficiency in mice, rats and lambs results in significant decreases in brain noradrenaline levels. It has been suggested that low concentrations of noradrenaline are due to a diminished activity of DBH [20]. Further studies examining catecholamine concentrations in different brain regions confirmed reduced noradrenaline levels and revealed increased dopamine (DA) concentrations due to DBH limitation in the medulla/pons region, areas often affected by depression. This limitation was also demonstrated in humans with a genetic copper deficiency, known as Menkes' disease [21]. Numerous studies have shown that a significant decrease in serum DBH activity can be observed in patients suffering from major depressive disorder as compared with controls [22,23].

However copper concentrations in the extracellular space of the brain are low (0.2–1.7 μ M), and in some brain regions it reaches a few hundred micromolar during neurotransmission. Released

Table 1

RDA – recommended dietary allowances, average daily level of intake sufficient to meet the nutrient requirements of nearly all (97–98%) healthy adult individuals (nutrient requirements of infants, children, the elderly, and women during pregnancy or lactation may be much different). AI, adequate intake; established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy. Based on report: Tolerable Upper Intake Levels for Vitamins and Minerals by the Scientific Panel on Dietetic products, nutrition and allergies (NDA) and Scientific Committee on Food (SCF), European Food Safety Authority, 2006.

Element	RDA/AI	Food sources
Copper (Cu)	1.1 mg/day (EU, 1993) 0.9 mg/day (US, 2001)	Organ meats, seafood, nuts and seeds, whole bran cereals, whole grain products
Selenium (Se)	55 μ g/day (EU, 1993; US, 2000) Lower limit of 40 μ g/day for a 65 kg man; of 30 μ g/day for a 55 kg women (WHO, 1996)	Seafood, organ meats, muscle meats, grain and cereal products, dairy products
Manganese (Mn)	1–10 mg/day (EU, 1993) 2–5 mg/day (US, 1994)	Grains, rice, nuts, tea
Iodine (I)	100–150 μ g (WHO, 1996)	Marine fish, shellfish, marine algae, seaweed, sea salt, dairy products, grain and cereal products, freshwater fish, poultry and meat, fruits, legumes, vegetables
Vanadium (V)	Not established	Seafood, black pepper, fennel seeds, mushrooms, parsley, shellfish, spinach

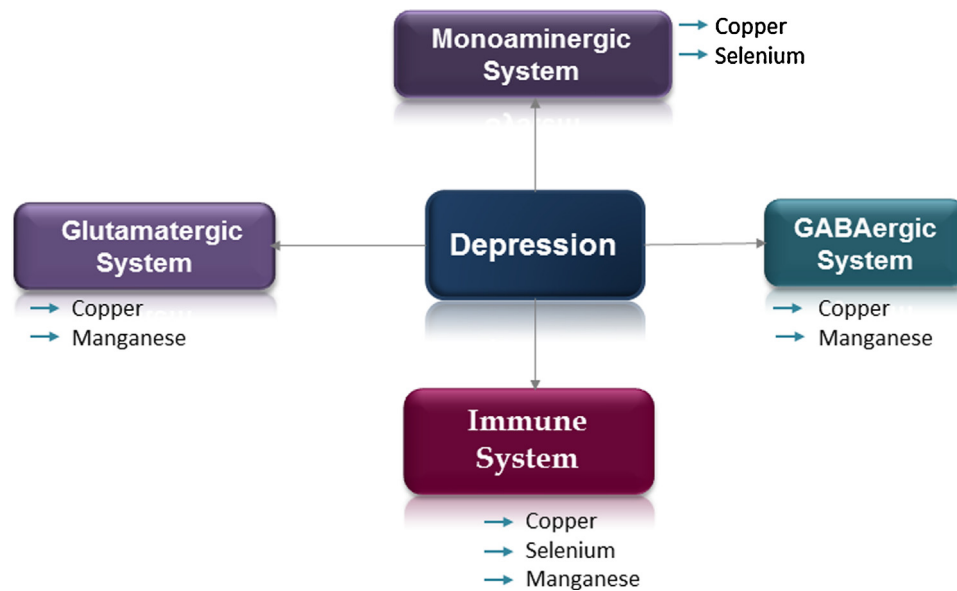


Fig. 1. Systems involved in the pathophysiology of depression. Depression has a diverse effects on different neurotransmitter or immune systems. Many elements have an effect on the monoaminergic system (copper, selenium) and glutamatergic or gabaergic system (copper, manganese). Appropriate levels of elements such as copper, selenium and manganese, regulate the immune system, which is also involved in depressive disorder.

copper may inhibit NMDA, AMPA and GABA receptor function at concentrations ranging from low nanomolar for GABA receptors, to micromolar for AMPA and NMDA receptors [24–27]. Alterations in glutamatergic and GABAergic transmission represent current fundamental etiologic and therapeutic aspects of mood disorders, particularly anxiety and depression.

About 65% of the plasma copper is bound to ceruloplasmin, a widely recognized positive acute phase (AP) protein [11,12]. In recent years it has been shown that major depression is accompanied by activation of the inflammatory response system

and an acute phase response, as indicated by an increase in serum levels of positive AP proteins [28,29]. Increased serum concentrations of ceruloplasmin suggests another potential role of copper in the course of depression.

Several studies investigated serum copper concentrations in depressed humans. Narang et al. [30], Manser et al. [31], Schlegel-Zawadzka et al. [32] as well as Schlegel-Zawadzka and Nowak [12] showed that serum copper levels were significantly higher in depressed patients as compared to controls, *i.e.* by 14%, 22% and 21%, respectively (for review see Table 2). Moreover, it was proven

Table 2

Clinical research on serum copper levels in depression.

Study design	Number of participants	Age [years]	Questionnaire used to identify mood disturbances	Method used to estimate amount of copper	Results	References
A case–control study	31 cases 62 controls	n/a	Copper n/a (diagnosed patients attending the outpatients neuropsychiatric clinic)	Plasma copper measurements (atomic absorption spectrophotometry)	The plasma copper levels in depressed patients were significantly higher as compared to controls (by 22%)	[31]
A case–control study	35 cases (21 males, 14 females) 35 controls	n/a	Hamilton depression rating scale	Plasma copper measurements (atomic absorption spectrophotometry)	The plasma copper levels in depressed patients were significantly higher as compared to controls (by 14%). After recovery, copper levels decreased significantly (by 15%)	[30]
A case–control study	19 cases 16 controls	n/a	Hamilton depression rating scale	Plasma copper measurements (atomic absorption spectrophotometry)	The plasma copper levels in depressed patients were significantly higher as compared to controls (by 21%)	[18]
A case–control study	31 cases 15 controls	n/a	Hamilton depression rating scale	Plasma copper measurements (atomic absorption spectrophotometry)	Antidepressant treatment significantly reduced serum copper levels	[11]
Cross-sectional analysis	902 (328 males, 574 females)	30–60	n/a (patients diagnosed at Pfeiffer Treatment Center in Illinois)	Plasma copper measurements (atomic absorption spectrophotometry)	Women with a history of post-partum depression exhibited significantly increased serum copper levels	[32]

that antidepressant treatment significantly reduced serum copper levels [28,30]. Another clinical study reported elevated serum copper levels in women with a history of post-partum depression (PPD) [33].

Contrary to clinical studies, the results of animal models of depression revealed no alterations in serum copper as compared to controls. However, chronic treatment of rodents with antidepressant drugs (citalopram, imipramine) or electroconvulsive shock (ECS) led to significant changes in serum and brain copper concentrations. Citalopram and imipramine significantly decreased serum copper levels without altering brain concentrations, whereas chronic ECS treatment increased hippocampal and cerebellar copper levels [12].

Several studies were performed to investigate the potential correlation between plasma concentration ratios of selected essential elements and severity of affective disorders. Most commonly such research concerned Zn/Cu [11,34,35], Fe/Cu [14] or Mg/Cu [36] inter-relationships in serum samples. It also remains for future research to determine whether therapy designed to normalize serum copper levels can benefit depressive patients.

Selenium

Selenium is a trace element that is widely distributed throughout human body. Its total amount in adult humans differs between regions – selenium levels range between 13 and 20.3 mg in the USA, but only 3 and 6.1 mg in New Zealand. Mean level 6.6 mg was found in Germany and approximately 5.2 mg in Poland [37]. A dietary selenium intake of 16 µg per day for women and 21 µg per day for men, taking into account body weight, is the lower limit recommended by World Health Organization (WHO). The seleno-cysteine form of selenium is incorporated into selenoproteins, most of which have so far uncertain function [38]. Selenoproteins such as glutathione peroxidases, thioredoxin reductases and selenoprotein P, are known to protect from lipoperoxidation and oxidative cell damage [39]. Recent studies have shown that depression is associated with increased levels of oxidative stress biomarkers which suggests that oxidative stress may be a significant factor in the pathogenesis of depression [40–43]. Selenium, which is also incorporated into iodothyronine deiodinases (DIOs), is essential for proper synthesis and metabolism of thyroid hormones [38]. It has

been long recognized by clinical investigators that thyroid function is associated with neuropsychiatric manifestation, such as mood disorders, cognitive dysfunction and other psychiatric symptoms [44]. Metabolism of selenium in the brain differs from other organs – during phases of reduced consumption and thus decreased levels of selenium, selenium is preferentially retained in the brain [44], and selenium deficiency was also shown to alter dopamine turnover rate in animal model [45].

Antidepressant-like effects of several organoselenium compounds have been investigated in animal models of depression. Administration of methyl-phenyl-selenide (CH₃SePh) reduced immobility time in the forced swim test (FST) (25 and 50 mg/kg *ip*) and in the tail suspension test (TST) (50 mg/kg) in mice. It was also suggested that this compound acts through interaction with the dopaminergic system [46]. Brüning et al. in their study showed that *m*-trifluoromethyl-diphenyl diselenide (*m*-CF₃-PhSe)₂, which is a selective inhibitor of monoamine oxidase A activity, was able to reduce immobility time in FST in female mice (50 and 100 mg/kg *po*). This effect was explained by interaction with the serotonergic and opioid systems [47]. A different compound known as Ebselen [2-phenyl-1,2-benzisoseleazol-3(2H)-one] decreased immobility time in FST in mice (10 mg/kg *sc*), but did not show any effect in TST (10–30 mg/kg *sc*), which concluded that Ebselen's antidepressant-like activity may be dependent on interaction with the dopaminergic and noradrenergic systems [48]. Jesse et al. investigated the possible antidepressant effect of bis selenide [(Z)-2,3-Bis(4-chlorophenylselenanyl)prop-2-en-1-ol]. They observed reduced immobility time both in the FST and TST in mice (0.5–5 mg/kg *po*) [49].

Studies on human populations investigated the relationship between selenium and the risk of depression, and have provided inconsistent results (Table 3). Recently Johnson et al. [50] analyzed data from 585 participants from a study of rural health in West Texas and found that higher groundwater selenium levels were associated with fewer symptoms of depression. They also highlighted the interaction between glutathione peroxidase 1 gene polymorphism and selenium exposure [50]. Another study showed that higher selenium levels were associated with lower Geriatric Depression Scale (GDS) scores [51]. However, when cognitive functioning was adjusted to the model, the effect was no longer

Table 3
Methodological summary of the listed publications – human population studies, focused on selenium supplementation (*) or on general selenium intake (**).

Study design	Number of participants	Age [years]	Questionnaire used to identify mood disturbances	Method used to estimate amount of selenium	Results	References
Double-blind placebo controlled trial	501 (448 included in the analysis)	60–74	Profile of Mood States–Bipolar Form (POMS-BI)	Selenium Plasma selenium measurements	Supplementation of selenium significantly increased plasma selenium level. There were found no differences in mood scores after six months of supplementation.	[53]*
A nested case–control study	18 cases 298 controls	≥20	Structured Clinical Interview for DMS-IV-ITR, Non-patient edition (SCID-I/NP)	Dietary selenium intake estimation using food frequency questionnaire together with anthropometric and lifestyle measures	A low dietary intake of selenium was associated with increased likelihood for <i>de novo</i> MDD	[52]**
Cross-sectional analysis	1737	65	Geriatric Depression Scale (GDS)	Selenium measurements from nail samples	Higher level of selenium was correlated with lower score on GDS questionnaire After adjusting of cognitive function, the association between selenium level and mood score, was not significant.	[51]**
Cross-sectional analysis	585	≥40	GDS	Estimation of selenium amount using Geospatial Inform System (GIS)	Higher level of groundwater selenium was correlated with lower score on GDS questionnaire.	[50]**

significant. Data from a nested case–control study of Pasco et al. [52] supports the hypothesis that lower dietary intake of selenium (<8.9 µg/MJ/day) is associated with a higher risk of *de novo* major depressive disorder.

Another interesting role of selenium is in the prevention of postpartum depression, which is a common mental health problem that affects approximately 6.5–12.9% of women during the first postpartum year [54]. It was shown that prenatal selenium intake from supplements is protective against depressive symptoms [55], although the mechanism behind the possible effects of selenium on postpartum mood disorders are unknown.

Manganese

Manganese (Mn) is an essential trace element, which can be found in air, water and food. Manganese can be absorbed either by inhalation or absorption through the gastrointestinal tract (3–8%), and its absorption is inversely related to the level of iron and calcium in the diet. It is present in most human tissues, but the highest concentrations of manganese are found in the liver, kidney, pancreas, and adrenal glands. According to the Agency for Toxic Substances and Disease Registry, the proper level of manganese in the blood is 4–14 µg/l. The Council for Responsible Nutrition in 2013 set a dose for chronically used supplements of manganese at 10 mg per day.

Manganese is an essential nutrient for the body. It plays role in the immune system and has also been associated with cancer prevention, as it is an important component of manganese superoxide dismutase (MnSOD, SOD-2) [56]. Moreover, manganese participates in the formation of connective tissue, bones, blood clotting factors, sex hormones, fat and carbohydrate metabolism, calcium absorption, blood sugar regulation, and is essential for normal brain and nerve function [57,58]. It accumulates mainly in the liver and the brain, particularly in the basal ganglia and globus pallidus. Abnormal concentrations of manganese in the CNS are associated with neurological disorders similar to Parkinson's disease [59].

As mentioned above, manganese is an important component of MnSOD, which is the primary antioxidant enzyme that protects cells from oxidative stress by catalyzing the dismutation of superoxide to hydrogen peroxide and oxygen in the mitochondria. Studies indicate that this enzyme protects cells from apoptosis and prevents the release of free radicals during excessive glutamatergic activity in the hippocampal CA1 and CA3 region, respectively [60,61]. It has been demonstrated that baseline levels of SOD-2 were decreased in patients during the depressive phase of bipolar disease, compared to healthy controls [62]. Furthermore, 30-days of treatment with fluoxetine increased the level of this enzyme [62]. Interestingly, studies showed that in patients suffering from major depression, a reduction in volume of prefrontal cortex and hippocampus may be connected with changes in the concentration of SOD-2 [63]. It is worth mentioning that proper incorporation of manganese into SOD-2 is an important determinant for the functional integrity of the enzyme. It has been shown that in cells deficient in manganese transporter, a loss of SOD-2 activity was noticed [64]. As Mn is essential for SOD-2 activity and low levels of this enzyme were reported in depressed patients, it can be concluded that low levels of manganese may also contribute to the development of depression, but this issue needs further studies.

On the other hand, many studies showed that manganese can be a neurotoxic agent and its toxicity was predominantly observed after chronic inhalation of high levels or, less often, following accidental ingestion of large quantities of the element. Manganism may, in early stages, manifest itself with increased anxiety, insomnia and irritability [65]. Jain and Ferrando reported a case of a welder suffering from *locura manganica* (a discrete Parkinson-like

syndrome that often occurs with chronic exposure to Mn), who showed, among others, the symptoms of depression [66]. Furthermore, it has been shown that the level of manganese is significantly elevated in patients suffering from generalized anxiety in comparison to healthy controls [67]. Studies indicate that in the CNS high levels of manganese tend to accumulate in astrocytes, altering glutamate homeostasis and eliciting excitatory neurotoxicity [68]. It is commonly known that glutamate is removed from the synaptic cleft by astrocytes and converted to glutamine, which is then released for uptake by neurons, and converted back to glutamate in glutamatergic neurons, or GABA in GABAergic neurons. It has been reported that high levels of Mn contribute to the impairment of glutamate–glutamine cycling, by deregulation of their turnover in astrocytes, resulting in the alterations in glutamate and GABA synthesis [69]. As glutamate and GABA dysfunction are connected with many psychiatric disorders, including anxiety and depression, which often occur in the early stages of manganism, it is very likely that high levels of manganese may also play some role in the development of mood disorders [70–72].

It is worth noting that there seems to be a link between the exposure to high levels of manganese and cognitive impairment. It has been proved that individuals exposed to manganese in working environments show cognitive alterations, including poor performance in neurobehavioral tests related to motor skills, mainly those requiring alternate or quick hand movements [73]. Furthermore, in male subjects exposed to inorganic manganese a significant alterations in audioverbal short-term memory capacity and slowed reaction time were reported [74,75]. Occupational exposure has also been correlated with altered working memory process [76]. Interestingly, Zou et al. reported a decreased plasma brain-derived neurotrophic factor (BDNF) level, which correlated with cognitive impairment in workers exposed to occupational manganese [77]. It is well known that low blood BDNF levels, among others, are associated with depression [78]. Although most experimental data comes from studies on occupational groups exposed to high levels of manganese (welders, miners, or workers in processing facilities), there are also reports concerning the negative effects of Mn exposure on cognitive functions in non-occupationally exposed individuals. Studies performed on this cohort of adults have shown both poor performance in motor tests [79] and a decrease in memory and learning associated with higher blood manganese levels [80,81]. Solís-Vivanco et al. reported the relationship between high levels of Mn exposure in the air and the presence of attention impairments in adults, however they did not find any relationship between Mn exposure and the prevalence of depression [82]. Similar results were obtained by Bowler et al. but this study reported other mood alterations such as increased anxiety, nervousness, irritability, emotional disturbance and aggression in individuals with higher levels of manganese [83]. In tests evaluating short-term memory, hand skills and visuoperceptual speed children exposed to high levels of manganese in drinking water obtained significantly lower results compared with the control group [84].

Iodine

Iodine is a trace element that is an essential component of thyroid hormones. The total amount in the human body ranges between 15 and 20 mg [85], and the recommended intake is 100–150 µg/day to ensure proper thyroid function. Iodine deficiency is considered as the most common cause of hypothyroidism worldwide [86]. Thyroxin (T4) binds to thyroid hormone receptor (TR) and is converted to 3,5,3-triiodothyronine (T3). In the brain the transformation is catalyzed by the type 2 deiodinase, which is a selenoprotein expressed in glial cells [87]. Severe deficiency of

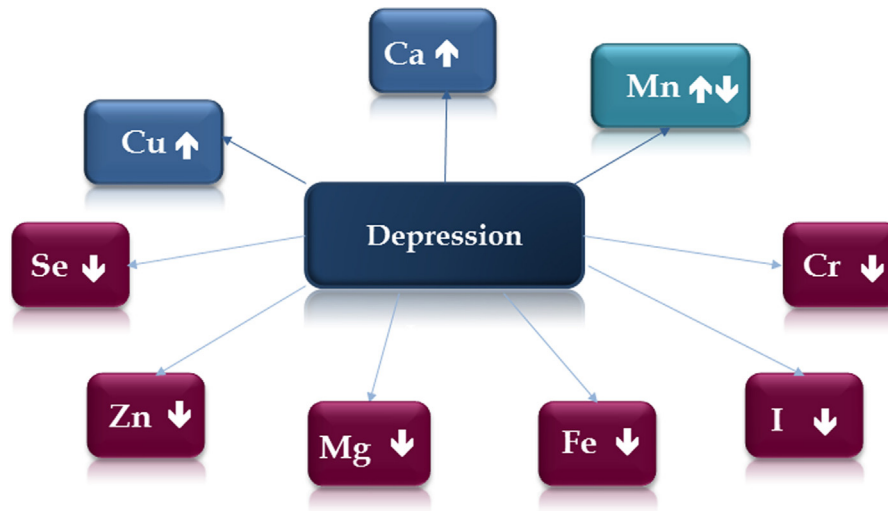


Fig. 2. The involvement of trace elements in the pathophysiology of depression—graphical summary of Part I and Part II.

iodine or thyroid hormones during fetal and early postnatal life may lead to permanent alterations in brain development and could cause mental retardation [85]. It was shown that hypothyroidism is associated with mood disorders [88,89] cognitive and affective disturbances [90] and memory impairment [91]. However, the relationship between anxiety disorders and hypothyroidism is speculative [88,92]. The study of Jorde et al. presented no evidence for neuropsychological dysfunction in subjects with subclinical hypothyroidism [93].

In animal models of mild hypothyroidism induced by two weeks of iodine-free diet, rats displayed depressive-like behavior with increased immobility time in FST [94]. Montero-Pedrazuela et al. [95] showed in their study that hypothyroidism impaired hippocampal neurogenesis in adult rats and this also correlated with abnormal behavior in FST. Also the relationship between depression and subclinical hypothyroidism in animal model was investigated [96]. After hemi-thyroid electrocauterization rats displayed increased immobility time in the FST and TST, but did not present any significant abnormalities in sucrose preference test.

Vanadium

Vanadium (V) is an ultra trace element, but its exact role in humans has been not yet defined. There is around 1 mg of vanadium in the body of an average person weighing 70 kg [97], and the daily requirement in the diet is not known. Most foods contain low concentrations of vanadium, but the largest quantities can be found in seafood, black pepper, fennel seeds, mushrooms, parsley, shellfish and spinach. Many studies confirm that vanadium exerts different insulin-mimetic and anti-diabetic effects [97–99], and it has been shown that the prevalence of depression in patients suffering from diabetes is much higher than in the general population. There has been one report suggesting that a novel vanadium complex (vanadium-enriched *Cordyceps sinensis*) may be beneficial in preventing depression in patients with diabetes [100]. The authors suggest that improved metabolic control achieved by vanadium may improve mood, but this hypothesis needs further studies [100].

Conclusions

In the present and previous review we focused on the role of trace elements such as zinc, magnesium, iron, chromium, lithium

and calcium [1], copper, manganese, selenium, iodine and vanadium. Many of these elements are involved in the function and homeostasis of serotonergic, noradrenergic, dopaminergic, glutamatergic and gabaergic systems, which are closely connected to depression and anxiety.

Trace elements are required for normal body function, and a deficiency or overabundance may lead to a diverse range of diseases, including psychiatric disorders (Fig. 2). Nowadays, strongly modified food and polluted environment may cause deficiency of trace elements, which often should be supplemented. Some of these elements, such as zinc or zinc/copper ratio, were proposed as a state marker of depression. Supplementation of elements such as zinc, magnesium or selenium was found to enhance commonly used antidepressants, or even found to produce antidepressant effects. These results show the important role trace elements play in psychiatric health.

Conflict of interest

All authors have participated sufficiently in this paper to take public responsibility for its content. Neither this manuscript nor one with substantially similar content or research under my (our) authorship has been published or sent for publication elsewhere. The customary listing of sources of support and institutional affiliations on the title page of a manuscript is proper and does not imply a conflict of interest.

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