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Magnesium for treatment-resistant depression: A review and hypothesis

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SUMMARY

Sixty percent of cases of clinical depression are considered to be treatment-resistant depression (TRD). Magnesium-deficiency causes *N*-methyl-D-aspartate (NMDA) coupled calcium channels to be biased towards opening, causing neuronal injury and neurological dysfunction, which may appear to humans as major depression. Oral administration of magnesium to animals led to anti-depressant-like effects that were comparable to those of strong anti-depressant drugs. Cerebral spinal fluid (CSF) magnesium has been found low in treatment-resistant suicidal depression and in patients that have attempted suicide. Brain magnesium has been found low in TRD using phosphorous nuclear magnetic resonance spectroscopy, an accurate means for measuring brain magnesium. Blood and CSF magnesium do not appear well correlated with major depression. Although the first report of magnesium treatment for agitated depression was published in 1921 showing success in 220 out of 250 cases, and there are modern case reports showing rapid terminating of TRD, only a few modern clinical trials were found. A 2008 randomized clinical trial showed that magnesium was as effective as the tricyclic anti-depressant imipramine in treating depression in diabetics and without any of the side effects of imipramine. Intravenous and oral magnesium in specific protocols have been reported to rapidly terminate TRD safely and without side effects. Magnesium has been largely removed from processed foods, potentially harming the brain. Calcium, glutamate and aspartate are common food additives that may worsen affective disorders. We hypothesize that – when taken together – there is more than sufficient evidence to implicate inadequate dietary magnesium as the main cause of TRD, and that physicians should prescribe magnesium for TRD. Since inadequate brain magnesium appears to reduce serotonin levels, and since anti-depressants have been shown to have the action of raising brain magnesium, we further hypothesize that magnesium treatment will be found beneficial for nearly all depressives, not only TRD.

Introduction

Neuropsychiatric disorders account for 36% of all non-communicable conditions, are the leading cause of all disability (more than twice that of cardiovascular diseases and malignant neoplasms) in the United States and Canada, with depressive disorders causing 40% of all neuropsychiatric disorders [1]. Major depression is expected to affect up to 25% of the American population at some point in their lives. Patients suffer in many areas of their lives, including sleep, eating, relationships, school, work, and self-image.

Increasing incidence of depression

Americans are developing major depression at higher rates and younger ages than ever before [2]. People born around 1900 rarely had childhood or early adult depression and only about 1% ever developed depression. People born between 1935 and 1944 had a 1% incidence of depression by age 15, a 2% rate of depression by age 25 and 9% incidence by age 45. People born in 1955, had a 1% incidence of depression by age 15, a 6% incidence by age 25, and a lifetime incidence of 25%. The onset of depression has greatly increased in incidence, and it is affecting people much earlier in their lives during the late 20th century and early 21st century than before the 20th century [2].

Classical depression treatments

Among those who seek professional help for clinical depression, some patients find relief for their condition using selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), tricyclic anti-depressants, herbal 5-HTP, omega-3 EFAs and various medical and psychiatric treatments. The clinical efficacy of current anti-depressant drug therapies is unsatisfactory; anti-depressants induce a variety of unwanted side effects, and, moreover, their therapeutic mechanisms are not clearly understood. Thus, a search for better and safer agents is continuously in progress [3].

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Treatment-resistant depression

A large proportion of the burden caused by depression is attributable to treatment-resistant depression (TRD). TRD itself is common, as high as 60% if TRD is defined – as it probably should be – as absence of remission from psychiatric medical and drug treatment. Duration and severity of illness are higher in TRD. In the short term, TRD is highly recurrent with as many as 80% of those requiring multiple treatments relapsing within a year of achieving remission. For those with a more protracted illness, the probability of recovery within 10 years is about 40%. Patients with TRD are more likely to suffer from comorbid physical and mental disorders, to experience marked and protracted functional impairment, and to incur higher medical and mental healthcare costs. Thus, in order to reduce the substantial burden caused by depression, TRD is one of the central focuses of medical research [4].

Hypothesis

We hypothesize that there is a different cause for TRD relative to treatable depression, a cause perhaps resulting from changes in the diet, and that magnesium-deficiency is involved as the main factor. For a long time it was not accepted that food could have any influence on brain structure and its function including cognitive, mood and intellectual development. However, it is now very certain that magnesium plays important roles in all the major metabolisms in oxidation–reduction and in ionic regulation, among other roles in the brain [5]. Experience taught us the value of bioavailable oral magnesium in effectively and rapidly treating depression [6] and we hypothesized that magnesium treatment would be broadly effective, be of wide clinical benefit in TRD and reports of its efficacy would be readily and widely found in the literature. We searched for reviews and found that there were none that were comprehensive and all inclusive, and that such review was needed.

Methods

To prepare this review, which we purport to be a comprehensive and all inclusive English-language review, we conducted a PubMed/Medline search for the terms magnesium and depression (1309 articles – only 76 related to mental health), magnesium and: "affective disorders" (40 articles), "treatment-resistant depression" (0 articles), "clinical depression" (0 articles), "major depressive disorder" (13 articles), and "major depression" (15 articles). The neurobiochemistry of magnesium and depression was reviewed mainly using neuroscience textbooks and a few of the 1232 related journal articles found on PubMed/Medline in a search for magnesium and NMDA. This review includes all related PubMed/Medline literature found prior to October 26, 2009, and is believed to not exclude any article for any reason. There was some overlap in the above searches.

Results

Against the wide-spread belief that Western countries are the best fed people on planet Earth, we found evidence that intake of magnesium is inadequate in many Western countries and especially in the diets of depressives [7] perhaps explaining the cause of TRD.

Food and magnesium

We found that magnesium intake has steadily declined over the preceding century, due to the practice of refining grain to make processed foods, making dietary choices low in magnesium-rich foods, strong chemical sequestration of metals during food processing and complete removal of minerals from drinking water processed by distillation and reverse osmosis. Only 16% of the original magnesium and 24% of the zinc found in whole wheat remains in refined wheat processed foods [8]. These circumstances reduced the average bioavailable magnesium consumption from 450 mg in the 19th century and before to 250 mg per day or less in the 20th and early 21st centuries, resulting in significant and unhealthy magnesium-deficiency in the majority of the population [9]. Approximately 68% of US adults consume less than the American recommended daily allowance (RDA) of magnesium (420 mg/day for men, 320 mg/day for women), with 19% consuming less than half of the RDA [7].

Food and excitotoxins

Conversely, extensive marketing and resultant consumption of excitotoxic glutamates and aspartates have greatly increased over the same period, even though there is a strong connection between dietary and endogenous excitotoxin excess and neurological dysfunction and mental illness [10,11].

Neurobiochemistry of magnesium

An examination of the role of magnesium in the neuron provides some insight into the cause and possible treatment of TRD. Weston in 1921 reported that Meltzer and Auer first showed in 1905 that the primary effect of magnesium treatment upon nerve cells was that of paralysis without any preceding excitation, and the effect seemed to be exclusively of an inhibitory character [12].

Magnesium and energy

Magnesium participates in numerous enzymatic reactions including all reactions that involve the formation and utilization of adenosine-5′-triphosphate (ATP) in energy metabolism [13]. Whenever neurons cannot generate sufficient ATP to keep their ion pumps working properly, membranes depolarize and excessive Ca^{2+} leaks into cells, triggering the synaptic release of glutamate, which further depolarizes neurons, further raising intracellular Ca^{2+} which causes even more glutamate to be released repeating in endless cycles [14] resulting in neuronal dysfunction and depression.

Magnesium dynamics

Intracellular concentrations of Mg^{2+} are about four times extracellular and are regulated by several systems including ion pumps and intracellular binding sites [15]. The blood–brain barrier and choroid plexus regulate CSF and brain Mg^{2+} against acute changes in Mg^{2+} concentrations, however during extended periods of Mg^{2+} deficiency brain levels of Mg^{2+} decrease [15]. Inadequate central nervous system (CNS) concentration of Mg^{2+} has a critical level below which neurological dysfunction occurs [15,16]. The interchange of Mg^{2+} between the cerebrospinal fluid, extracellular fluid, and bone is more rapid and dynamic than has been previously believed [16], although the brain does not share in this interchange. This effect is magnified by hypertrophied parathyroid gland being associated with significant skeletal depletion of magnesium. Magnesium, much like calcium, has a large presence in bone, and it has a negative feedback relationship with the parathyroid gland. A critical decline in CNS magnesium may occur when the skeletal buffer system – orchestrated largely by the parathyroid glands – is activated by an increase in serum calcium in the presence of long-term magnesium-deficiency [17], moving Mg^{2+} ions from the CSF into the blood and eventually into the bone with