Magnesium and major depression

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Abstract

The treatment of major depression is still a major unmet medical need in the majority of patients. Sixty percent of cases of MD are treatment-resistant depression (TRD), showing that classical treatments for MD are poorly effective to non-effective. Magnesium has been largely removed from processed foods, especially refined grains, in the Western world harming the brain and causing mood disorders. Magnesium deficiency causes N-methyl-D-aspartate (NMDA) coupled calcium channels to be biased towards opening which causes neuronal injury and neurological dysfunction, which we believe results in MD. Oral administration of Mg to animals produced antidepressant-like effects that were comparable to those of antidepressant drugs. Cerebral spinal fluid (CSF) Mg has been found low in suicidal TRD. The first report of Mg treatment for agitated depression was published in 1921 showing success in 220 out of 250 cases. One 2008 randomized clinical trial showed that Mg was as effective as the tricyclic antidepressant imipramine in treating MD. Intravenous and oral Mg protocols have been reported to rapidly terminate MD safely and without side effects. Brain Mg deficiency reduces serotonin levels, and antidepressant drugs have been shown to have the action of raising brain Mg. Excessive calcium, glutamate and aspartate intake can greatly worsen MD. We believe that – when taken together – there is more than sufficient evidence to implicate inadequate dietary Mg as contributing to the cause of MD, and we suggest that physicians prescribe Mg for its prevention and treatment.

Incidence of major depression

Neuropsychiatric disorders account for 36% of all non-communicable illnesses. They are the leading cause of all disability (more than twice that of cardiovascular diseases and malignant neoplasms) in the United States and Canada. Depressive disorders cause 40% of all neuropsychiatric disorders (World Health Report, 2004). Without magnesium (Mg) treatment, major depression (MD) is expected to affect up to 25 percent of the American population at some point in their lives. Besides core symptoms of depression, i.e. depressed mood and lack of energy, other symptoms may vary, but nevertheless have strong effects on patient quality of life. These include increased or decreased appetite and weight and sleep disturbances, in particular difficulties falling asleep, maintaining sleep and, in melancholic depression, early morning awakening. Emotional reactivity can be very different with increases in sensitivity to social challenges, easy upset, sadness on the one hand and an unresponsive mood, which leaves patients with "feelings of feelinglessness" on the other hand. Feelings of guilt and sadness can be very pronounced, leading to suicidal ideation and finally suicide itself.

Increasing incidence of depression

Americans are developing MD at higher rates and younger ages than ever before. People born around 1900 rarely had childhood or early adult depression and only about one percent ever developed depression. People born between 1935 and 1944 had a one percent incidence of depression by age 15, a 2 percent rate of depression by age 25 and 9 percent incidence by age 45. People born in 1955, had a one percent incidence of depression by age 15, a 6 percent incidence by age 25, and a lifetime incidence of 25 percent (Meyer and Quenzar, 2005).

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 (Meyer and Quenzar, 2005). The reasons for these findings are not quite clear, but inadequate

dietary Mg is prevalent in America and is the most likely cause. There is probably a real increase in depression, coupled with a change in diagnostic habits, which has to do with the element of stigma. Lower stigma leads to a higher rate of diagnosis. Modern antidepressant drugs are better tolerated than first generation antidepressive treatments which, in terms of a risk-benefit analysis, makes less severely affected subjects candidates for psychopharmacological intervention. Unfortunately, antidepressant and anti-anxiety medications commonly in use have a tendency to promote suicide, especially in young people (Stone, 2009).

Classical depression treatments

Among those who seek professional help for clinical depression, some patients find relief for their condition using therapies bases on modification of monoaminergic systems. Newer generation antidepressants are now used and they include selective serotonin reuptake inhibitors (SSRIs), combined serotonin/noradrenaline reuptake inhibitors, and drugs which interact with monoaminergic receptors such as mirtazapine. First generation antidepressants like monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants are now rarely used because they are not well tolerated.

Treatment-resistant depression

A large proportion of the burden caused by depression is attributable to treatment-resistant depression (TRD). Only half of patients who are treated with a first line pharmacological therapy of an SSRI respond and only 30% experience remission (Trivedi *et al*, 2006). If a second drug also fails, a commonly used criterion for TRD is fulfilled. Treatment-resistant depression 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 a central focus of medical research (Fekadu *et al*, 2009). Apart from the complete non-responders there are many patients who fulfill criteria of "remission" but still have symptoms severe enough to interfere with their quality of life, i.e. residual symptoms (Nierenberg *et al*, 2010). Besides quality of life implications of residual symptoms, their presence predicts relapse of depressive disorders. This shows that even in the group of remitted subjects an unmet medical need remains.

Markers and risk factors of major depression

Major depression is a disorder which has both psychological and physiological causes and risk factors. Because psychological causes may trigger pathophysiologic mechanisms, there is overlap. In this article we are focusing primarily on physiology of MD with some reference of MD as a stress-related disorder. We also focus on systems which may be related to Mg-dependent regulation.

Biological markers of depression or depression-vulnerability

There are certain biomarkers which have been described in patients with depression and in "high risk" populations; meaning those who never have had MD, but who have a close relative that does (Lauer *et al*, 1995; Modell *et al*, 1998). These biomarkers include an increased stress hormone axis (HPA-axis), a higher density of rapid eye movements in sleep EEGs and less slow-wave sleep (SWS), particularly in the first sleep cycle (Krieg *et al*, 2001). Lower SWS and higher HPA axis activity were also identified as risk factors for a relapse in patients, who were in remission after a depressive episode (Hatzinger *et al*, 2004). Not all studies confirm these points, in particular with regard to HPA axis findings (Ising *et al*, 2005). This suggests biological variability in subjects with a risk for depression.

A more recently indentified potential marker for depression is aldosterone, which is increased in patients with depression (Emanuele *et al*, 2005; Murck *et al*, 2003). This may be of importance, as aldosterone is a primary regulator of Mg. As both aldosterone and cortisol are regulated by ACTH there could be a correlation between the two phenomena (Murck, 2002).

Typical sleep disturbances occur in MD including falling asleep, staying asleep and early morning awakening, or hypersomnia and excessive napping. Sleep EEG patterns have been indentified for MD. Rapid eye movement (REM) sleep changes occur with a shorter latency to the first occurrence of REM, a higher number of eye movements during REM sleep, i.e. a higher REM density, and in some subjects reduced duration of slow wave sleep (Steiger and Kimura, 2010; Thase *et al*, 1997). Subjective reports of sleep disturbances may also be predictive of a depressive episode. A review of eight epidemiol-ogical studies concluded that insomnia, lasting for a period of 2 weeks, was predictive for development of depression in the subsequent 1 - 3 years.(Riemann and Voderholzer, 2003). Insomnia at baseline and 1 year post-baseline compared with those with no sleep complaints was strongly predictive of a future MD (adjusted odds ratio, OR=39.8; P<0.01) (Ford and Kamerow, 1989). Another study (van den Berg *et al*, 2007) found a similar association for hypersomnia. Sleep disturbances and neuroendocrine data are correlated, in particular hypercortisolism is correlated with the number of awakenings and reduced SWS (Hubain *et al*, 1998).

Several cardiovascular factors, especially low systolic blood pressure, are risk factors for MD (Gilmore *et al*, 1995; Paterniti *et al*, 2000). Subjects with MD show lower heart rate variability (HRV) (Udupa *et al*, 2007). Insomnia is related to a lower HRV (Spiegelhalder *et al*, 2010). Heart rate variability appears to increase with successful treatment. Reduced HRV is a risk factor for depression in patients with coronary heart disease (Pizzi *et al*, 2008).

Inflammatory markers are an additional area of potentially useful predictive markers for depression. Plasma IL-6, TNFα and prostaglandin E2 (PDE2) are of relevance (Murck *et al*, 2004; Zorrilla *et al*, 2001). Elevated inflammatory markers are related to non-response to the most frequently used antidepressants today, i.e. SSRIs (Eller *et al*, 2008; O'Brien *et al*, 2007). Anti-inflammatory agents appear to have anti-depressant effects, as in the case of TNFα-antagonists (Uguz *et al*, 2009), cyclooxygenase inhibition (Muller *et al*, 2006) and omega-3 fatty acids (Murck *et al*, 2004).

Changes in dietary magnesium

Against the wide-spread belief that Western countries have the best fed people on planet Earth, there is evidence that serious deficits in dietary Mg in the Western world are related to an increased risk for MD and biological markers of depression. For a long time it was not accepted that food could have any influence on brain structure or its function including cognitive, mood and intellectual development. It is now absolutely certain that Mg plays vital roles in all major metabolisms in oxidation-reduction and in ionic regulation among its other roles in the brain (Bourre, 2006) and in mood disorders Dietary magnesium intake has steadily declined over the preceding century, due to: (1) the practice of refining grain to make processed foods, (2) making dietary choices low in magnesium-rich foods such as whole grains, rice and wheat bran, nuts, seeds, chocolate, peanuts, peanut butter and green leafy vegetables, (3) strong chemical sequestration of metals during food processing and (4) complete removal of minerals from drinking water processed by distillation, de-salination and reverse osmosis so prevalent in the Middle East, Australia and elsewhere. Only 16% of the original Mg and 24% of the original zinc found in whole wheat remain in refined wheat (Anonymous, 2002). These circumstances reduced average bioavailable Mg 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 Mg deficiency in the majority of the population (Seelig and Rosanoff, 2003). Approximately 68% of U.S. adults consume less than the U.S. recom-mended daily allowance (RDA) of Mg (420 mg / day for men, 320 mg / day for women), with 19% consuming less than half of the RDA (Jacka *et al*, 2009). Deficiency of dietary Mg has been related to depressive disorders (Rasmussen *et al*, 1989; Hashizume and Mori, 1990). The pathological signs of Mg-deficiency and possible reasons for its development have been reviewed earlier (Morris, 1992; Durlach, 1984; Durlach *et al*, 1995; Durlach *et al*, 1997; Durlach, 2002). A recent study confirmed the epidemiological relationship between low dietary Mg intake and the risk of developing depression (Jacka *et al*, 2009).

Conversely, extensive marketing and resultant consumption of excitotoxic glutamates and

aspartates have very 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 (Blaylock, 1999; Walton *et al*, 1993).

Regulation of brain magnesium

The concentration of Mg within the brain results from a highly regulated process. Its concentration in cerebrospinal fluid (CSF) is higher than that in plasma, pointing to the existence of active transport systems between these compartments (Morris, 1992). Magnesium moves out of CSF into blood by passive diffusion and bulk filtration (Oppelt *et al*, 1963). These dynamics result in relative stability of intra-cerebral Mg concentration even in case of Mg depletion. Up to 40 days of Mg depletion led only to a small global intra-cerebral decrease in Mg concentration in rats, however important regional differences existed (Poenaru *et al*, 1997). The brainstem seemed particularly vulnerable to Mg depletion. Increasing Mg administration had no strong influence on CSF Mg concentrations. Only small changes in CSF Mg after prolonged supplementation were reported in dogs (Kemeny *et al*, 1961; Schain, 1964). However, chronic dietary Mg deficits led to proportional changes in CSF and brain cellular Mg (Chutkow, 1974).

It is of importance to note that metabolism of Mg depends on endocrine parameters. Administration of aldosterone led to an enhancement of urinary excretion of Mg in humans (Horton and Biglieri, 1962). Acute β-adrenergic stimulation with adrenaline or salbutamol reduced plasma Mg in humans (Whyte *et al*, 1987), pointing to an adrenergic mechanism of Mg regulation. The parathyroid is influenced by Mg in its function, and it regulates Mg levels and distribution (Zofkova and Kancheva, 1995). Inadequate central nervous system (CNS) concentration of Mg^{2+} has a critical level below which neurological dysfunction occurs (Yasui *et al*, 1997; Langley, 1991).

Acute emotional stress, which involves an activation of the SNS and the HPA axis, led to an increase in Mg excretion in humans (Grases *et al*, 2006) and experimental animals (Altura *et al*, 1992), the latter resulting from reduced tissue and serum Mg. Swim stress in animals led to an activation of several stress hormone systems and an increase in Mg in plasma, but a decrease in brain Mg (Poleszak *et al*, 2005). This shows that tissue Mg is more relevant than plasma Mg. Stress induced decrease in brain Mg could be counteracted with additional administration of the tricyclic antidepressant imipramine. This finding is complicated by observation that co-administration of both imipramine and Mg has a beneficial behavioral effect, but does not counteract the reduction of brain Mg-concentration resulting from swim stress. Therefore, increased sympathetic nervous system (SNS) activity could lead to increased Mg excretion. This suggests that stressful activities result in lowered Mg content of the CNS and potentially and increased risk of depression.

Similarly, thyroid function is related to Mg regulation. In 135 un-medicated patients with mild to moderate major depressive disorder, a significant correlation between mean serum Mg^{2+} levels and mean circulating T4 thyroid level was observed. There was no significant correlation between any other thyroid indices and either serum Mg^{2+} or Ca^{2+}. The thyroid axis is known to regulate Mg metabolism possibly by regulation of transport of Mg^{2+} from extracellular to intra-cellular fluid compartments. For T4, and to a lesser extent serum Mg^{2+}, the most consistent changes were observed with response to anti-depressant treatment (Joffe *et al*, 1996).

Changes of serum magnesium in major depression

Our following review of serum Mg and depression shows greatly conflicting results, perhaps because 99% of Mg is intracellular with only 1% being found in serum (Mann and Truswell, 2002), and perhaps because some of the work used magnesium oxide, which is not bioavailable (Firoz and Graber, 2001; Lindberg *et al*, 1990; Walker *et al*, 2003; Enya *et al*, 2004).

In patients with low serum Mg, depressive symptoms have been observed (Hashizume and Mori, 1990). Deficits of Mg may result from inadequate intake, malabsorption, or renal loss of Mg that occurs in certain disease states such as alcoholism and diabetes, and with certain drug therapies (antidiuretics, aminoglycosides, fluoro-

quinolones, cisplatin, digoxin, cyclosporin, amphotericin B) (Morris, 1992). Resulting Mg-deficiencies may lead to depressive symptoms which are secondary to an underlying somatic disease, like diabetes mellitus (Barragan-Rodriguez *et al*, 2007). In depressed patients, an early study reported a decrease in total plasma Mg, but not in ionized Mg, with an increase in total Mg occurring after treatment with electroconvulsive therapy or tryptophan (Frizel *et al*, 1969). Higher serum (Bjorum, 1972) and plasma Mg levels have been reported in patients with recurrent depression independent from their actual state, i.e. as a trait marker (Cade, 1964; Widmer *et al*, 1992). Widmer stressed the importance of gender and clinical subtypes of depressive disorder. They also reported an association between increases in plasma Mg and severity of depression and of plasma cortisol (Widmer *et al*, 1995). Another group reported that depressive symptoms were positively correlated with serum Mg in longstanding depression and remission, but not in acute depression (Linder *et al*, 1989). A further study shows the same relation in patients with unipolar depression (Hasey *et al*, 1993). In other studies, this finding could not be confirmed (Naylor *et al*, 1972; George *et al*, 1994). A further study compared serum Mg and serum Ca/Mg ratio of 145 drug free patients with MD. They compared MD patients to a group of non-mood disordered patients without finding any difference between groups (Young *et al*, 1996). In another study no changes in absolute values of plasma Mg concentration could be observed in patients with a variety of psychiatric disorders. An association between the amount of Mg plasma disturbance (either higher or lower than normal) and severity of clinical disturbance was shown (Kirov *et al*, 1994). Research subjects, who did not meet criteria of any specific psychiatric disorder, were studied to explore their experiences with depression, anxiety and stress in relation to Mg-levels. Subjects were not differentiated on the basis of high vs. low Ca/Mg ratios, but on the basis of Mg tertiles. The group in the middle tertile had the lowest levels of depression and stress in comparison to upper and lower tertiles (Jung *et al*, 2010). A more recent study found a decreased serum Mg concentration in patients with more severe depression (Hamilton depression score > 23), whereas no change was observed for less severely affected subjects (Nechifor, 2009). The studies of Kirov *et al*, 1994 and Jung *et al*, 2010 could point to the fact that closer specification of depressive disorders may be required. Gender differences (with lower concentrations in women) exist in plasma Mg concentrations in patients with depression (Herzberg and Herzeberg, 1977; Herzberg and Bold, 1972; George *et al*, 1994), possibly contributing to the variability seen in the mentioned studies. Furthermore, it appears that medication should be controlled, as anti-depressant compounds have been reported to influence Mg-metabolism, as measured as changes in erythrocyte Mg concentration in the course of antidepressant treatment (Nechifor, 2009). It is unclear if this is a direct effect of the compounds (sertraline and amitriptyline) or an indirect effect of clinical improvement of subjects.

In patients with depression an increase in aldosterone concentration has been observed (Murck *et al*, 2002a). Under physiologic conditions an increase in aldosterone concentration should lead to an increased excretion of Mg . Reports of an increase in serum Mg points to a disturbance in Mg regulation in these patients, which may also involve a higher grade of Mg mobilization from intracellular pools. On the other hand a deceased sensitivity of mineralocorticoid receptors (MR), which are the primary responsible receptor for aldosterone regulation in the kidney, has been reported. This points to a potentially complex Mg dysregulation. It would be of importance to determine the relationship between Mg and aldosterone concentration in order to clarify this issue.

In contrast to peripheral changes in plasma or serum, changes within the CNS point to a brain Mg-deficiency. In subjects with MD, a decrease in CSF Mg concentration has been confirmed (Banki *et al*, 1986; Banki *et al*, 1985) A more recent study found an increase in the Ca/Mg ratio of CSF in patients with depression (Levine *et al*, 1999). Most recently, postmortem studies in patients that had depression showed a reduced Mg concentration in brain tissue (Nowak *et al*, 2010). Human brain Mg measurements by phosphorus nuclear magnetic resonance spectroscopy (NMR) have demonstrated a reduced Mg concentration in depressed patients who were refractory to treatment with an SSRI (Iosifescu *et al*, 2005).

This method provides the best means to determine Mg-concentrations in specific anatomical areas in living brains

Functional impact of magnesium

An examination of the role of Mg in neurons provides some insight into the cause and possible treatment of MD. Weston in 1921 reported that Meltzer and Auer first showed in 1905 that the primary effect of Mg treatment upon nerve cells was that of paralysis without any preceding excitation, and the effect seemed to be exclusively of an inhibitory character (Weston, 1921-22).

Monoaminergic systems and magnesium

The locus coeruleus (LC) is the principal anatomical structure of the noradrenergic system. Its activity is related to that of the SNS, and it shows overactivity in melancholic depression. Magnesium infusion led to an increase in circulating norepinephrine (NE) in humans in one study (Leppert *et al*, 1994), whereas no changes in catecholamines were reported in another (Zofkova *et al*, 1993). Magnesium-deficiency on the other hand increased plasma catecholamines in response to noise stress in rats (Caddell *et al*, 1986). Mice selectively bred for low blood Mg levels showed a significantly higher brain NE content without a change in dopamine, HVA, and serotonin compared to those with high Mg levels (Amyard *et al*, 1995). This was interpreted as a higher sensitivity to stress in mice with low blood Mg content. A suppressive effect of Mg on LC activity has been demonstrated (Shiekhattar and Aston-Jones, 1992) and interpreted as an NMDA antagonistic mechanism. Magnesium deficiency reduced behavioral activity from dopaminergic activation by amphetamine and apomorphine (Kantak, 1988). The antidepressant-like effects of Mg are dependent on its interaction with serotonergic, noradrenergic and dopaminergic receptors (Cardoso *et al*, 2009).

Glutamatergic system and magnesium

Magnesium depletion is specifically deleterious to neurons by causing NMDA-coupled calcium channels to be biased towards opening (Sapolsky, 1992) At normal neuronal resting membrane potentials, pores of the NMDA glutamate-gated ion channels are blocked by Mg^{2+} ions (Bear *et al*, 2001; Mark *et al*, 2001; Kandel *et al*, 1995; McMenimen, 2006). The ion channel of the NMDA receptor complex is subject to voltage-dependent regulation by Mg ions (Mark *et al*, 2001; Alberts *et al*, 2002; Decollogne *et al*, 1997). Importantly, different types of NMDA receptors exist, on the basis of their constitution subunits. Besides NR1subunits, which are constitutional for all subtypes, NR2 elements define their diversity. NR2 exists in flavors of NR2A, NR2B, NR2C and NR2D. Of particular interest, NMDA receptors which contain NR2A and NR2B receptors, are more sensitive to voltage sensitive Mg block (Kuner and Schoepfer, 1996). This direct interaction of Mg with the NMDA receptor intracellular mechanism influences its activity. In hippocampal synaptosomes, the Mg block of the NMDA dependent ion channel is removed by activation of protein kinase C (PKC) without changing membrane potential (Pittaluga *et al*, 2000). Intracellular administration of a PKC agonist accordingly potentiated NMDA receptor function in cultured hippocampal neurons (Xiong *et al*, 1998). This could lead to a feed-forward cycle; an NMDA dependent Ca^{2+} current may increase PKC activity leading to further release of the Mg-block of the NMDA dependent ion-current. Mg also has a direct influence on PKC function. The catalytic subunit of PKC requires Mg as a cofactor (Hannun and Bell, 1990), and deactivation of PKC by adenosine triphosphate (ATP) depends on presence of Mg (Wolf *et al*, 1985). Besides influencing NMDAergic neurotransmission, Mg depletion affects hippocampal excitability via non-NMDAergic Ca currents, which can also be suppressed by verapamil, a Ca-channel blocker (Pohl *et al*, 1992; Walden *et al*, 1992). These findings, when put together, illustrate several possible mechanisms for Mg to limit the kindling state via modulation of different elements of the Ca–PKC-second messenger system.

Normally operating NMDA receptors admit into neurons only the amount of Ca^{2+} that is vital to their function, but abnormally functioning NMDA receptors (due to inadequate Mg) increase influx of cellular Ca^{2+} beyond manageable levels leading to the generation of toxic reactive oxygen species and of toxic amounts of nitric oxide (NO) radicals (Blaylock, 1999; Mark, 2001; Carafoli, 2005).

Stress hormone systems (HPA and RAAS) and magnesium

Acute intravenous Mg administration decreased adrenocorticotrophic hormone (ACTH) secretion in healthy subjects (Murck and Steiger, 1998), but did not lead to a change in cortisol secretion (Zofkova *et al*, 1993; Murck and Steiger, 1998). Subchronic oral administration of Mg in healthy elderly subjects led to a decrease in cortisol concentration without a change in ACTH (Held *et al*, 2002). Chronic oral administration of high-dose Mg leads to considerable reductions in cortisol and lowered stress responsiveness. Both effects are in line with a decrease in central corticotropin-releasing hormone release, but differential effects occur at the level of the adrenal cortex. The possibility of an NMDA antagonistic effect of Mg has been discussed in context of hippocampal function. Both systems also influence endocrine regulation and hypo-thalamic activity.

Inflammatory system and magnesium

Magnesium depletion has been studied for its effects on inflammatory markers. Feeding rats Mg-depleted food led to a nearly 3-fold increase in plasma interleukin 6 (IL-6), a significant increase of fibrinogen and other acute phase proteins and a significant reduction in Zn (Malpuech-Brugere *et al*, 2000). Mg-deficiency also amplifies endotoxin-induced lethality in rats, which was correlated with increased TNFα production (Malpuech-Brugere *et al*, 1999). In rat models Mg deficiency led to an increase in thromboxane TBX2 and prostaglandin E2 (PGE2) (Nigam *et al*, 1986; Soma *et al*, 1988). For a review of the correlation between Mg-deficiency and inflammatory changes, see Nielsen *et al*, 2010. Of considerable importance is that NMDA-ergic mechanisms may activate inflammatory mechanisms (Muller *et al*, 2009).

Magnesium in animal and human research

In the following sections we summarize data concerning effects of Mg in animals and preliminary findings in humans. One important issue to keep in mind is the unresolved question: Does Mg treat a Mg deficit or is Mg to be regarded as a pharmacological agent, i.e. independent of a preexisting deficit? We will not be able to answer this question on the basis of current data. Nevertheless, in the long run it is important to identify specific characteristics of subjects who may benefit from Mg treatment. Most subjects having MD treatable with magnesium also have, or have had, other disorders which are also treatable with magnesium (Eby, 1999-2010).

The functional systems described above have been recognized as potential pharmacological targets for treatment of depression. All current commercial antidepressants are based on the hypothesis of a monoamine-dysfunction. On the other hand, NMDA receptor antagonists, and in particular those for the NR2B subtype, have demonstrated clinical efficacy (Berman *et al*, 2000; Preskorn *et al*, 2008). The HPA axis has long been recognized as a potential target for antidepressants (Flores *et al*, 2006; Holsboer, 2000; Jahn *et al*, 2004). More recently anti-inflammatory mechanism-like COX-2 inhibitors (Muller *et al*, 2006) and TNFα-antagonists (Uguz *et al*, 2009) have been demonstrated. In the following text we report behavioral effects by Mg in animal models as well as human clinical data. The specific mechanism of these effects by Mg has yet to be elucidated.

Animal Models and magnesium

Animal models have provided insight into roles of stress on Mg status, effects of Mg deficiency, and effects of Mg treatment in depression.

Mg is involved in behavioral control in rats. Mg deficiency led to a reduction in offensive behavior and an increase in defensive behavior (Kantak, 1988). Apomorphine- and L-amphetamine mediated behavior was suppressed by Mg deficiency, suggesting that Mg is an important factor for the stimulatory action of catecholamines possibly at the postsynaptic site. In the forced swim test, a screening test for possible antidepressive potency of substances, Mg reduced immobility similar to the nor-epinephrine reuptake inhibitor imipramine (Decollogne *et al*, 1997). Compared to control mice fed a normal diet, mice receiving a low Mg diet (10% of daily requirement) for several weeks displayed increased immobility time in the forced swim test, indicating enhanced depression-like behavior. In addition, partial magnesium-

depletion feed increased anxiety-related behavior in the light/dark and open field test, while locomotor activity and motor coordination was not influenced. Magnesium depletion led to depression and anxiety-related behavior in mice. These changes due to Mg deficiency were prevented by coadministration of desipramine or hypericum extract (Singewald *et al*, 2004). A dependency of intracellular Mg and behavioral regulation appears to exist. Mice selected for low vs. high erythrocyte Mg levels showed pronounced neurobiological differences (Henrotte *et al*, 1997). Low Mg mice showed a more restless behavior, a more aggressive behavior under stressful conditions and higher brain and urine NE levels compared to mice with high erythrocyte Mg. It is not clear if a correlation between intraerythrocyte and intraneuronal Mg concentration exists.

Of importance is that Mg deficiency leads to depression-like changes and that Mg administration has "therapeutic" effects on depression-like behavior. Magnesium administration led to anxiolytic effects in the elevated plus-maze, and antidepressant like effects in the forced swim test (Poleszak *et al*, 2004). In stressed rats Mg and imipramine acted synergistically on immobility time as measured in the forced swim test, i.e. non-efficacious doses of both compounds combined led to a positive behavioral response (Poleszak *et al*, 2006). The mechanism is complex and appears to involve NMDAergic (Poleszak *et al*, 2008), GABAergic (Poleszak 2008) and serotoninergic (Poleszak 2007) modulation.

Human studies and magnesium

There are a number of open label studies on therapeutic effects of Mg administration in treating depression, depression-like and anxiety illnesses. As early as 1921 a report on the therapeutic effect of Mg was published in the first issue of the American Journal of Psychiatry (and immediately forgotten). In 220 out of 250 doses of magnesium sulfate (one or two cc of a 25 or 50 percent solution) given hypodermically to 50 patients having agitated depression, with several having various other agitated states, treatment caused patients to relax and sleep from four to six hours resulting in a 90% success rate for Mg (Weston, 1921-22). The sedative side effects from giving too much Mg were quickly and easily reversed by giving similar amounts of calcium chloride given hypodermically.

Later studies showed a beneficial effect of Mg in treatment of rapid cycling bipolar disorder in ten patients (Chouinard *et al*, 1990) in an open label study for periods up to 32 weeks. Magnesium was found to produce clinical results at least equivalent to those of lithium in 50% of patients. The possibility that Mg could replace or improve efficacy of lithium without side effects as a preventive treatment of manic-depressive illness was suggested.

In tests of magnesium lactate and vitamin B6 (pyridoxine) in treatment of 25 patients with anxiety-depression and epilepsy, the combination exerted positive non-specific influences on patient's mental state, especially with regard to affective disorders. Effects emerged on day 14 of treatment and achieved a statistically significant level by day 28. Treatment was well tolerated and did not cause any side effects (Kalim *et al*, 2004).

Further support comes from improvement of a subject with the rare hereditary disorder of Gitelman's syndrome, which leads to a lack of reabsorption of electrolytes including Mg. Intravenous supplement of magnesium sulfate (20 mEq/day dissolved in 100 ml normal saline given over 2 hours each day for 3 days) immediately terminated both depression and paraesthesia, suggesting that hypomagnesemia played a role in clinical manifestations of depression (Enya *et al*, 2004). Oral magnesium oxide treatment was ineffective and promoted diarrhea. Magnesium oxide should not be given in treatment of mental illnesses since it is not bioavailable generally and it does not pass the blood-brain barrier.

Mood stabilizing properties of Mg have been demonstrated in case reports in patients with mania (Pavlinac *et al*, 1979). In an open study with intravenous magnesium sulfate used as a supplementary therapy to lithium, benzodiazepines, and neuroleptics in mania, marked clinical improvement was observed in the 10 patients included. This was accompanied with a significant reduction in requirement for neuroleptic and benzodiazepine (Heiden *et al*, 1999). In a further open trial in mania the effect

of a Mg–verapamil combination was compared with that of verapamil alone, and the combination was superior for manic symptoms (Giannini *et al*, 2000).

Four case histories were presented showing rapid recovery (less than 7 days) from MD using 125–300 mg of magnesium (as glycinate and taurinate) with each meal and at bedtime (Eby and Eby, 2006). Related and accompanying mental illnesses in these case histories, which were also benefited, included traumatic brain injury, headache, suicidal ideation, anxiety, irritability, insomnia, cocaine, alcohol and tobacco abuse, hypersensitivity to calcium, short-term memory loss and IQ loss . Post partum depression appeared prevented in several case histories with Mg, wherein the patients had previously had severe PPD without Mg. The possibility that magnesium deficiency is the main cause of most MD and related mental health problems including IQ loss and addiction was described as enormously important to public health and was recommended for immediate further study (Eby and Eby, 2006). Magnesium was claimed usually effective for treatment of depression in general use by depressives reading "Depression Treatment: A Cure for Depression using Magnesium?" on the Internet (Eby, 1999-2010).

To date only one randomized double-blind, controlled trial exists concerning effects of Mg administration on MD. Magnesium chloride ($MgCl_2$) was evaluated in the treatment of newly diagnosed depression. Twenty-three elderly patients with type 2 diabetes and hypo-magnesemia were enrolled and randomly allocated to receive orally either 50 mL of a $MgCl_2$ 5% solution (equivalent to 450 mg of elemental Mg) or 50 mg imipramine daily during 12 weeks. Widowhood or divorce in the previous six months, alcoholism, degenerative illnesses of the nervous central system, previous or current treatment with antidepressants, chronic diarrhea, use of diuretics, and reduced renal function were exclusion criteria. At end of the treatment period, depression scores were identical between groups. Serum Mg levels were significantly higher in subjects receiving $MgCl_2$ than in subjects receiving imipramine, $p = 0.0005$ (Barragán-Rodríguez *et al*, 2008).

Several studies in indications which involve depressed mood exist. In a double-blind, placebo-controlled trial in chronic fatigue syndrome, a disorder related to atypical depression, weekly intramuscular injections of 2ml magnesium sulfate (50%) or placebo for 6 weeks showed significant superiority of Mg over placebo on energy levels, pain, and emotional reactions as measured by the Nottingham health profile score (Cox *et al*, 1991).

In another placebo controlled study of premenstrual syndrome, which has depressive elements, effects of oral Mg for the duration of two menstrual cycles was observed (Facchinetti *et al*, 1991). The medication consisted of 3 x 360mg Mg in the form of Mg–pyrrolidone carboxylic acid. It was administered from day 15 of the menstrual cycle to onset of menstrual flow. Mg showed a significant superiority to placebo in the total score of the Menstrual Distress Questionnaire score and especially the cluster "negative affect". In the same indication, combination of 200mg Mg and 50mg vitamin B6, but not individual treatments alone, administered daily for the duration of one menstrual cycle in a Latin square design was superior compared to placebo on premenstrual symptoms as nervous tension, mood swings, irritability and anxiety (De Souza *et al*, 2000). Another study using a crossover design found only an improvement in symptoms related to fluid retention in women taking 200mg Mg or placebo in the second menstrual cycle (Walker *et al*, 1998).

Adverse effect of calcium in depression

Decreases in CSF calcium accompanied mood elevation and motor activation in depressed patients. Similarly, decreases in CSF calcium occurred during acute psychotic agitation or mania. Periodic recurrences of such agitated states were accompanied at their onset by transient increases in serum calcium and phosphorus. Several observations suggested that such serum ion shifts triggered the more enduring and opposite shifts in CSF calcium and, in turn, manic behavior. Progressive restriction of dietary calcium was earlier reported to mitigate and finally abolish both rhythmic rises in serum calcium and periodic agitated episodes. A modest oral calcium lactate supplement (approximately one additional U.S. Recommended Daily

Allowance) intensified agitation and worsened depression. In manic patients, symptomatology grew significantly and substantially worse during 2 to 6 weeks of oral vitamin D administration.

On the other hand, in 12 patients, subcutaneous injections of synthetic salmon calcitonin decreased serum calcium and phosphorus, increased cerebrospinal fluid calcium, and augmented depressive symptomatology. Salmon calcitonin, which lowers blood calcium levels, also decreased quantified motor activity, frequency and severity of periodic agitated episodes, serum creatine phosphokinase and prolactin, and nocturnal sleep, while vitamin D or calcium lactate raised them (Carman and Wyatt, 1979).
A dietary supplement of 500mg calcium immediately and severely worsened MD, which was extinguishable within one hour by orally treating with 400mg gel capsules of Mg as magnesium glycinate (Eby and Eby, 2006).

In a study of electrolytes in CSF from depressives, a positive correlation was found between calcium concentration and symptom severity in hospitalized depressed patients. CSF calcium levels tended to decrease as patients improved. In rapidly cycling patients, CSF calcium was higher during depression than during mania (Jimersom *et al*, 1979).

Major depression was found to be accompanied by hyperactivity of subcellular calcium signaling, and any means of reducing pathological neuronal calcium ion flow to reduce pathological nitric oxide NMDA neuronal output would have antidepressant effects (Paul, 2001). Hypercalcemia from excessive vitamin D intake, hyperparathyroidism or other causes has been suggested to lead to clinical depression by lowering brain Mg (Keddie, 1987).

Biomarkers of magnesium and magnesium-related functions

Although there is considerable interest in understanding roles of Mg in brain chemistry and explanation of its role there, we found little consensus as to the value of Mg measurements in blood (serum, plasma or cellular) as a diagnostic tool useful in treating depression. CSF concentrations of Mg in depression were also conflicted, although there appeared agreement that CSF Mg^{2+} values were low only in severe depression associated with suicide attempts supporting the notion that Mg would be useful specifically for TRD, which is often much more severe than treatable depression.

Since 99% of Mg is intracellular, serum Mg testing of the remaining 1% in serum produces misleading results (Mann and Truswell, 2002). Although serum values less than 0.9 mmol/Mg demonstrate Mg deficiency in non-depressives (Liebscher and Liebscher, 2004), it is often normal or elevated in depression. Consequently, serum tests are of negative utility due to their misleading nature, and red blood cell tests are also of questionable, perhaps negative, value. Although various tests for Mg deficiency and calcium excess appear desirable; the response to Mg treatment with calcium reduction is always the deciding criteria.

Brain compartments of Mg are isolated from blood and bone compartments requiring different analytical means. Measuring brain Mg can be safely accomplished in humans using phosphorus NMR spectroscopy (Iosifescu *et al*, 2008; Iotti and Maulcelli, 2008). This test needs to be validated by repeated trials as a reliable means to determine low brain Mg in diagnosis of low brain Mg as cause of MD.

A health warning is therefore warranted regarding potential misinterpretation of "normal" serum Mg. In case of doubt restoration of Mg stores in deficient patients is simple, tolerable, and inexpensive and can be clinically beneficial (Ismail *et al*, 2010).

Recommendations concerning magnesium-supplementation

Dietary fibers affect intestinal absorption of Mg. Inulin, a prebiotic that supports bifidobacteria and lactobacilli, has been confirmed to be important in absorption of Mg in the large intestines (Scholz-Ahrens and Schrezenmeir, 2007; Rondón *et al*, 2008) nearly doubling Mg absorption and reducing tendency to diarrhea, but increasing gas, while taking Mg. Large doses of psyllium seed husks greatly reduced absorption of Mg (Asvarujanon *et al*, 2004) and gum arabic significantly increased both intestinal and renal excretion of Mg (Nasir *et al*, 2008), and

both should be avoided. Indole-3-carbinol (I3C) (200 mg/meal) was found in a case study to reduce greatly the necessity for frequent Mg treatment to prevent relapse (Eby and Eby, 2006).

Useful Mg compounds are those that have a sufficiently low first stability constant to be bioavailable and include: magnesium acetate, chloride, citrate, gluconate, glycinate, lactate, malate, oxalate, succinate, sulfate and tartarate (Furia, 1968). The bioavailability of magnesium oxide is extremely limited, ranging from 0 - 4% (Firoz and Graber, 2001; Lindberg *et al*, 1990; Walker *et al*, 2003; Enya *et al*, 2004). Studies in which magnesium oxide is used produce misleading results when compared with results obtained using other compounds of Mg for the same indication.

Future clinical research

We are concerned that there were only a few clinical trials of Mg for human depression found. We suggest that future trials be of larger populations in formal, double-blind, placebo-controlled clinical trials, or comparative trials against a proven antidepressant such as imipramine 50 mg daily. Only when evidence of efficacy has become clearer are physicians likely to adopt Mg for MD.

From reports reviewed herein, we suggest that in future clinical research in depression that the initial treatment utilize IV drip magnesium sulfate in the manner of Enya *et al*, 2004, (20 mEq/day dissolved in 100 ml normal saline given over 2 hours each day for 3 days) to provide an expected rapid (<3 days) initial induction of remission. Treatment is to be followed by an oral bioavailable Mg (125 – 300 mg 4 t/d) maintenance treatment in the manner of Eby and Eby 2006 or Barragán-Rodríguez 2008 using bioavailable Mg compounds with emphasis on magnesium glycinate and taurinate. Magnesium oxide must not be used since it is non-bioavailable (Firoz and Graber, 2001; Lindberg *et al*, 1990; Walker *et al*, 2003; Enya *et al*, 2004). During IV administration, cardiac monitoring should be performed. Protocols for IV administration of magnesium sulfate have been widely used for treatment of eclampsia. The antidote to magnesium overdose is calcium gluconate or calcium chloride. Since 99% of Mg is intracellular, serum Mg testing of the remaining 1% found in serum will produce misleading results (Mann and Truswell, 2002) and it should not be used in future research.

Impediments to success and precautions

We are concerned that there are some impediments to proper absorption of Mg in large therapeutic doses by the oral route with intestinal issues, especially inflammatory bowel disease (Galland, 1988) and diarrhea being primary concerns. Large doses of oral Mg without calcium may exponentially increase Candida albicans intestinal growth (Holmes *et al*, 1991), causing or worsening diarrhea and impairing absorption of Mg, while adding calcium may greatly and immediately worsen depression. Candida albicans overgrowth may be prevented or treated naturally by greatly reducing intake of sugars and treating with large amounts of Bacillus Coagulans probiotic and biotin. We are very concerned that magnesium oxide will be given with failure to respond becoming highly evident, thus damaging the reputation of Mg as an effective treatment for depression. Do not give magnesium oxide because it has been shown to be not bioavailable. Additionally, magnesium aspartate and magnesium glutamate have neurotoxic ligands and they must be avoided to prevent worsening depression.

Conclusions

Lack of definitive, large-scale, double-blind, placebo-controlled clinical trials is the limiting factor for making strong treatment recommend-ations using Mg. Countering that point of view is the good safety of Mg compared to side-effect prone antidepressant and anti-anxiety medications.

From evidence reviewed here and from the 2010 review by Eby and Eby, the relationship between low Mg intake as a risk factor for MD appear to have extremely important preventative and treatment implications. A dietary supplement of 600 to 800 mg/day Mg (other than magnesium oxide) should be a universal prevention strategy.

Mechanisms, which lead to CNS Mg depletion, should be further studied in an effort to discover

new targets and medication for MD. Evidence for a Mg-regulation effect of psychoptropic drugs already exists, however the exact mechanism is unclear. Reasonable candidates go beyond monoaminergic mechanisms and may include manipulation of the renin-angiotensin-aldosterone system and, less studied, specific Mg transport mechanisms. The best direct measurement of brain Mg is by phosphorus NMR spectroscopy, but this will probably be reserved for research purposes.

Although more research is clearly needed, we suggest that it is past time to give Mg in appropriate doses and to reduce intake of calcium, glutamate and aspartate for the prevention and treatment of MD, especially TRD, and anxiety, since we can expect rapid improvements in patient health and major reductions in patient expenses without side effects. We did not pay attention to those early Mg and brain pioneers Meltzer and Auer in 1905 and other magnesium researchers over the last 100 years and we may pay the price today.

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