

**ASSESSING A GAP IN THE BIOMEDICAL LITERATURE:****MAGNESIUM DEFICIENCY AND NEUROLOGIC DISEASE**Neil R. Smalheiser<sup>1\*</sup> and Don R. Swanson<sup>2</sup><sup>1</sup>Department of Pediatrics and<sup>2</sup>Professor of Information Sciences,University of Chicago, MC 5058, 5841 S. Maryland Avenue,  
Chicago, IL 60637 USA. \*corresponding author*(Accepted May 6, 1994)***SUMMARY**

Recent studies have focused great attention upon the role of NMDA receptor-mediated excitotoxicity in the pathogenesis of a variety of acute and chronic neurologic diseases, and upon the role of endogenous Mg ions in regulating this process. Yet, very few studies have sought to ascertain whether exogenous, e.g., dietary, manipulations of Mg levels can modulate brain function or the expression of neurologic diseases (apart from hyperexcitability and seizures that are elicited directly when Mg levels are extremely low). We argue that this issue is important, and should be addressed in existing animal models of acute and chronic CNS insults.

**KEY WORDS:** magnesium, NMDA receptor, excitotoxicity, diet, information retrieval**INTRODUCTION**

The present paper is the fourth in a series (1-3) which has utilized information retrieval techniques (4,5) to identify important, but neglected, problems inherent within the biomedical literature. Such strategies do not rely on having prior expert knowledge of a given field, but instead analyze co-occurrences of words in titles, and co-citation patterns, of papers within that field. Of particular interest are "complementary-but-disjoint" pairs of research topics that show certain related patterns of word usage, yet lack any cross-citation and have not been related directly

to each other by scientists (5). For example, a previous study of the migraine literature revealed that papers on migraine employ a word usage pattern which is related to that of the literature regarding magnesium -- significantly more so than for most other bioactive substances -- even though no single paper had both "migraine" and "magnesium" in its title, and even though no prior studies had attempted to ascertain whether migraine was associated with an alteration in magnesium levels in blood or brain. Since such an association was quite plausible on biological grounds, it was suggested that this was worthy of further investigation (2). Indeed, a link between magnesium and migraine was subsequently confirmed experimentally (6-16).

In the course of analyzing the magnesium-related literature further, we noticed that neuroscientists have studied the role of endogenous Mg ions in the pathogenesis of neurologic diseases extensively, yet -- apart from investigations of hyperexcitability and seizures that are directly produced by states of severe Mg deficiency -- very few studies have examined the effects of exogenous (particularly dietary) manipulations of Mg on brain function (see Appendix). On the other hand, nutritionists, clinicians and experimental pathologists have studied Mg widely as a dietary constituent and as a risk factor in the pathogenesis of cardiovascular diseases -- but strangely, apart from cerebrovascular problems such as stroke, very few have examined neurologic diseases (see Appendix). Why have possible links between dietary Mg intake, Mg deficiency and brain function been neglected in the midst of such intensive scientific activity?

Unexamined topics, or "gaps", can exist in the biomedical literature for many reasons. Some topics lack inherent importance; for others, suitable experimental tools or model systems are not available, or negative scientific evidence is compelling. For some topics, it is just a matter of time before they are investigated. However, as presented below, our analyses suggest that the relation of dietary Mg intake (or other causes of Mg deficiency) to neurologic diseases has been neglected largely because of scientific specialization. Although findings and proposals exist within both neuroscience and nutritional/clinical literatures which favor taking the topic seriously, these findings have been poorly integrated or publicized across fields. Such failures of synthesis across specialties are pandemic within science, and appear to be an inevitable consequence of the immense size and rapid growth of the scientific literature (5).

### **Mg deficiency and the brain**

Magnesium is a major regulator of membrane excitability and calcium channel function. Recently, the discovery that Mg acts as a noncompetitive inhibitor of the NMDA receptor (17,18) has uncovered its widespread involvement in neurologic disease. Intracellular and extracellular pools of Mg modulate NMDA receptor-dependent excitotoxic damage to neurons -- though NMDA

receptor-mediated excitotoxicity was first studied as a mediator of acute neuronal death, it has been increasingly implicated as a common pathogenetic mechanism in a variety of both acute and chronic conditions (19-25), as it appears that relatively modest abnormalities in a neuron's ability to handle excitotoxic stress contribute to a more subacute expression of neurodegeneration (see also ref. 26). Thus, even relatively small abnormalities in Mg levels within critical brain sites should be in a position to influence the rate of progression of any ongoing excitotoxic process. Magnesium is also an important regulator of cerebral blood flow and distribution through its influence upon cerebral vascular tone (27).

Studies of grazing animals, laboratory animals (particularly rats) and human volunteers have elucidated the sequelae of Mg deficiency induced by severe dietary restriction, which include seizures and other manifestations of hyperexcitability (28,29). Other CNS alterations have been noted as well, including pathologic changes of neurons (30,31) and disordered sleep patterns (32). But it is not widely known that the neurologic risks associated with Mg deficiency can extend beyond its direct signs and symptoms. We were able to find two studies (33,34), both quite recent, which have examined whether the adverse effects of experimental CNS insults can be potentiated by Mg restriction. Both reported positive results:

- 1) McIntosh et al. fed adult rats (400-500 g) a magnesium-deficient diet for 14 days, sufficient to reduce total plasma Mg levels by 50% and intracellular brain free Mg levels by 15-20% as assessed by NMR. They found a dramatic deterioration of outcome after an experimental fluid-percussion traumatic brain injury; whereas no control rats died within 4 weeks post-trauma, 53% of Mg deficient rats died, and the survivors had significantly greater neurologic dysfunction (33).

- 2) Nakanishi et al. fed weanling mice a partially Mg-deficient diet (chow containing 24 mg/kg, vs. 300 mg/kg in controls) for 14 days, and found greatly decreased survival times among Mg-deficient animals after acute exposure to hypoxia. Although the Mg-deficient animals (and hippocampal slices derived from these animals) also exhibited tonic epileptiform activity when exposed to hypoxia, seizures were not the direct cause of death since several anticonvulsants effectively blocked seizure occurrence without affecting survival times (34).

The McIntosh et al. article has since been cited in 17 other papers (including self-citations), and Nakanishi et al. in one, primarily as providing further support for a role of endogenous Mg ions in the pathogenesis of brain trauma and epilepsy, respectively. However, neither of these two original articles, and only one of the citing papers (35), discussed explicitly the possibility that the results in Mg deficient animals might suggest a heightened state of risk in Mg deficient humans.

### **Mg deficiency in man**

In man, Mg deficiency is not restricted to the severely malnourished. Hypomagnesemia is prevalent in about 10% of patients in general hospitals; it is relatively common within certain groups such as the elderly, alcoholics, and diabetics (36,37), and those taking a variety of medications (e.g., furosemide or cis-platinum) (29). Many reports have suggested that Mg depletion has an adverse effect on the development of a variety of disorders, particularly those that involve the cardiovascular system (38-41).

A number of prominent workers have gone further, citing nutritional balance and epidemiologic studies to suggest that many people in the general population receive a diet that is barely adequate in Mg intake, and may be subject to increased longterm medical risks even in the absence of hypomagnesemia (29, 40, 42-45, 45a). These controversial proposals have been well publicized in the nutritional/clinical literature but hard evidence is lacking, not simply because of the difficulties inherent in human studies, but because major uncertainties exist in current understanding of clinical and laboratory assessment of Mg metabolism (29,46).

### **Studying the impact of mild Mg deficiency**

The nutritional/clinical literature has posed two important questions which, except as already noted, have not yet been considered in the neuroscience literature: "Does Mg depletion increase the incidence or worsen the outcome of disease states?" and "What is the minimal extent of Mg restriction which is associated with increased risk?" On the other hand, the neuroscience community has achieved a breakthrough in understanding how Mg modulates excitotoxic damage to neurons, and has provided animal models which have great potential for providing an objective, quantitative means of determining some of the neurologic risks associated with Mg deficiency. We propose that, by titrating the degree of dietary Mg restriction progressively from severe to mild, one should be able to assess whether the outcome of insults is measurably altered by otherwise subclinical degrees of Mg deficiency.

For example, in a straightforward extension of McIntosh et al. (33), different groups of adult rats could be fed for 14 days with commercially available chow containing different amounts of dietary Mg (levels of Mg in tap water either need to be measured, or controlled for by employing distilled water for drinking). These rats would then be measured for serum Mg levels, subjected to percussion trauma, and followed for mortality, neurologic dysfunction scores, and extent of histologic damage. A variety of other animal models could also be utilized in which excitotoxicity appears to play a central role in pathogenesis (25), such as ischemia, acute seizures, chronic seizures/kindling, kainic acid injections, or stab wounds. Rats or mice could also be subjected to



chronic mild Mg deprivation (47), perhaps in conjunction with quantitative models of chronic neurodegeneration such as lines of transgenic mice infected with prion diseases (48).

The results of Mg manipulations in animals cannot be directly equated to the situation in man. Yet since the overall syndromes of Mg deficiency are quite similar across the vertebrates, results obtained in animal models will need to be taken seriously in terms of their potential clinical and public-health implications, and should provide a starting point for assessing the likely extent of risk associated with Mg deficiency in humans.

### WHY DOES IT MATTER?

Physicians already screen certain classes of patients for hypomagnesemia, and are alert to covert Mg deficiencies in specific conditions such as alcoholism. Moreover, the possible benefits of elevating Mg levels acutely in patients following head trauma have been discussed in a number of recent reviews (e.g., 49). Why should neuroscientists go out of their way to look for additional longterm risks associated with Mg deficiency -- not only those associated with hypomagnesemia, but also those associated with mildly deficient states which may be more prevalent in the normal, apparently healthy population at large? Perhaps a historical example may be helpful. At one time, people with "malignant", or symptomatic, hypertension were known to be seriously ill, but those with "benign" hypertension were thought simply to be normal variants. After large-scale epidemiologic studies established that hypertension was a graded risk factor for a variety of diseases, "benign" hypertension itself became viewed as a disease, whose vigorous screening and treatment has had a dramatic impact on mortality and morbidity. By analogy, if one accepts that excitotoxicity participates in the pathogenesis of neurologic diseases over an subacute or chronic time course, one must consider seriously the notion that "benign" degrees of Mg deficiency may accelerate this process. However, unlike hypertension, mild Mg deficiency in humans cannot be diagnosed with a simple screening test. This point alone would be sufficient to impede epidemiologic studies. Thus, the investigation of experimental CNS insults in deficient animals appears to be the most practical means at present of assessing whether the Mg deficient state can influence neurologic diseases.

### APPENDIX

To document our claim that possible links between dietary Mg intake, Mg deficiency and brain function/neurologic disease have been neglected, searching for relevant articles was carried out in various databases. Only a few, scattered articles were found, that touched on one or another limited aspect of this problem. Yet the problem as a whole has not been reviewed previously in the literature, nor have the attempts to address it experimentally been systematic or cohesive.

Searches were made in MEDLINER<sup>®</sup>, EMBASE, BIOSIS<sup>®</sup>, AND SCISEARCH<sup>®</sup>. Papers were included that were written in languages other than English, but reliance upon database searching meant that the pre-1966 literature was largely ignored. Because of indexing omissions and word usage idiosyncracies, no literature search can retrieve all papers on a given subject; however, we have attempted to be systematic and diligent.

For example, in one search of MEDLINER<sup>®</sup>, 48,036 records were found in which the word "magnesium" appeared in the title, abstract, or subject heading field. Of these, 2,992 records also contained the word "diet", "diets", or "dietary"; words beginning with "supplement-" in the title or abstract; or contained the subject heading Diet. This group was further narrowed to 209 records that were indexed within Medical Subject Heading (MeSH) categories of Nervous System or Nervous System Diseases. These 209 records were examined for content. Not unexpectedly, most of these papers dealt with dietary factors other than Mg, and most of those concerning dietary Mg were related to direct signs and symptoms of severe deficiency states including hyperexcitability, tetany, and cerebrovascular effects. The remaining papers, including experimental studies, editorials, reviews and hypotheses, but excluding meeting abstracts, are briefly listed below.

A second type of search focused on magnesium deficiency. For example, all records were identified that met any of the following three criteria: 1) subject heading "magnesium deficiency" or with a word beginning "hypomagnes" in the title or abstract; 2) "magnesium" in the title or abstract within a 6-word vicinity of a word beginning with "defici" or "deplet" or "restrict" or "depriv"; 3) "magnesium" in any field and a word beginning "Mg" in the title or abstract within a 6-word vicinity of a word beginning with "defici" or "deplet" or "restrict" or "depriv". The result was then restricted to records indexed under the subject headings "Nervous System Diseases" or "Nervous System" or with any subject heading containing the word "nerve" or "brain". The 209 records found in the "diet" search described above were then excluded, leaving a set of 331 records which were examined directly. Altogether, 51 papers were identified from these and other searches, which fell into four topical groups:

**1. Beneficial effects of dietary Mg supplementation:** Improved learning in young and old rats (50). Ameliorated migraine headache (6,7,11,15,45). Protection against noise-induced hearing loss in humans (51). Reduced exacerbations in multiple sclerosis (52). Increased Mg in food and water was correlated with decreased incidence of ALS-PD complex in Guam over the past 30 years (53).

**2. Adverse effects of dietary Mg restriction in laboratory animals:** Neuronal damage (30,31). Reduced or unchanged levels of brain magnesium in Mg-restricted animals (47,54-56). Hearing

loss (57). Increased auditory brainstem response amplitudes (58). Increased protein oxidation (59). Hypokinesia, ataxia, and decreased caudate dopamine concentration (60). Embryotoxic effects on neural tube (61). Increased neurotoxic effects of gentamicin and salicylate (57), brain Al (62), and lead (63). Intracellular alkalosis in brain (64). Increased audiogenic stress responses (65,66). Reduction of brain ascorbic acid content (67). Increased brain dopamine and 5-hydroxyindole-3-acetic acid and decreased sleep in rats (68). Increased or unchanged levels of monoamines in Mg-deficient animals (69,70). Reduced numbers of Gomori-positive glia (71). Early increase in serum levels of substance P, followed by increases in inflammatory cytokines and histamine (72).

**3. Adverse effects of combined nutritional deficiencies:** Mg restriction worsened neuropathologic changes produced by combined nutrient deficiency (73-75). A diet low in Ca and Mg, but high in Al, decreased Zn concentration in soft tissues in rats (82), Mg content of the spinal cord in rats (76), and produced neurodegenerative changes in rats (31) and monkeys (77). Muscle pathology in rats fed a Ca-Mg deficient diet is similar to that of ALS patients (78). Rats fed a low Ca-Mg diet showed degeneration and Ca deposits in anterior horn cells (79). Rabbits and Japanese monkeys on low Ca-Mg, high-Al diet developed anterior horn cell pathology (79). Thiamine levels in nervous tissue unchanged in Mg-deficiency (80), but Mg-deficiency may increase thiamine refractoriness in Wernicke-Korsakoff encephalopathy (81).

**4. Risk factor in neurologic diseases:** a) Low Mg content was reported in ALS and MS patient autopsy tissue samples at 26 CNS sites (83,84,91,92). Based on these and other data, it was suggested that Mg deficiency may be a risk factor in multiple sclerosis (84). b) A hypothesis paper speculating on a link between Mg depletion and Alzheimer's Disease (85) was discussed in a letter-to-the-editor (86) and a review (87). Mg deficiency has also been discussed as a possible risk factor in schizophrenia (88), depression, and some organic psychoses (56,65). c) Mg deficiency decreased expression of experimental allergic encephalomyelitis (89). d) Mg deficiency has been associated with appearance of down-beat nystagmus (90).

The 51 articles just listed are "very few" in comparison with other magnesium-related literatures; for example, about 900 records in Medline deal with Mg and NMDA receptors. Fewer than one-fifth of the 51 articles were published in neuroscience journals, as defined by the ISI listing for Current Contents<sup>R</sup> (in contrast, three-fourths of the Mg-NMDA receptor papers were published in neuroscience journals). But there is another, more important reason why neuroscientists (and others) may not be aware of these 51 articles. Citation and co-citation analyses revealed that these papers were unusually isolated; they did not correspond to a pattern expected from scientists with a common specialized interest or from groups working on a common problem. Furthermore, no appreciable subset of them has previously been reviewed or analyzed as a group. Each of the 51 articles was searched for all subsequent citing articles in the entire literature covered by Scisearch<sup>R</sup>. Garruto et al. (1985) had been cited 68 times; Landfield and Morgan (1984) and Saul and Selhorst (1981) 24 times each; Chutkow and Grabow (1972) and Chutkow (1974) 20 times each; and all others 13 times or fewer. Next, all papers in the literature were identified that cited any two or more of the 51 articles: There were only 9 such papers, excluding self-citations, or 17 if self-citations are included. (This is unusually low, as seen by

contrast to a previous co-citation analysis of 63 articles on magnesium, defined by having common indirect linkages to the migraine literature, where 115 papers cited two or more of the 63 (2).) Moreover, excluding self-citations, no more than 4 of the 51 articles listed above were ever cited together, even in reviews.

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