Cardiovascular and Intestinal Responses to Oxidative and Nitrosative Stress During Prolonged Magnesium Deficiency

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Abstract: In rodents with dietary magnesium deficiency (Mg deficiency), hypomagnesemia, occurs leading to a rise in circulating substance P from neuronal tissues to trigger systemic inflammatory stress in cardiac and intestinal tissues. Sustained elevations of substance P may result from impaired neutral endopeptidase (NEP) activity due to reactive oxygen and reactive nitrogen species. Associated increase in intestinal permeability includes infiltration of WBC and endotoxemia, which can further amplify the systemic inflammatory response that leads to impaired contractile function associated with up-regulation of the cardiac CD14 endotoxin receptor. The neurogenic signal transduction pathways that we have identified in the pro-oxidant/pro-inflammatory processes found with prolonged hypomagnesemia are described in this report.

Key Indexing Terms: Magnesium deficiency; Hypomagnesemia; Substance P and substance P receptor blockade; Inflammatory/oxidative stress; Cardiac and intestinal tissues; Neutral endopeptidase; Systemic endotoxemia and endotoxin receptor; Cardiac dysfunction. **[Am J Med Sci 2011;342(2):125–128.]**

CLINICAL HYPOMAGNESEMIA

Hypomagnesemia can occur clinically as a result of restricted dietary intake, Mg^{2+}-wasting drug therapies and chronic disease status.[1] Persistent hypomagnesemia may increase cardiovascular risk; in those populations consuming low levels of Mg^{2+}, there is a greater risk of morbidity and mortality after an episode of myocardial ischemia.[1–4] Mg^{2+} wasting also occurs in patients with diabetes, the metabolic syndrome, alcoholism, HIV and many with cancer.[1,5] In a study of critically ill patients with cancer, one half had hypomagnesemia.[5] Hypomagnesemia is common in hospitalized intensive care patients, the mortality rate of acutely ill patients with hypomagnesemia is increased 2-fold.[6] Inherited disorders of Mg^{2+} wasting can also cause a progressive dilated cardiomyopathy.[7] Treatment of hypomagnesemia can be successful with proper intravenous and oral replacement therapy, but if left undiagnosed, the complications of systemic magnesium deficiency may be profound.

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ROLE OF NEUROPEPTIDES AND SUBSTANCE P RECEPTOR IN HYPOMAGNESEMIA

Our investigations with hypomagnesemic rodents led to the discovery that circulating levels of the pro-inflammatory neuropeptide, Substance P (SP),[8] were significantly elevated within a week after initiating a Mg^{2+}-deficient diet[9–11]; another neuropeptide that is found in C-fibers, calcitonin gene-related peptide, was also elevated concurrently with SP, indicating their probable release from sensory nerve fibers.[12] These elevations of SP and calcitonin gene-related peptide preceded increase in circulating white blood cells[13] and other circulating proinflammatory mediators.[9]

Table 1 lists the multiple organ systems affected by such neurogenic inflammation. We also found that this neuropeptide may induce many inflammatory/oxidative events, which eventually promote cardiomyopathy. Others have reported increases in PGE2,[14] circulating histamine[15] and erythema with pink ears[16] in Mg^{2+}-deficient rats. SP acting on neurokinin-1 receptors can stimulate rat endothelial cells, mast cells, macrophages and white blood cells, including T cells.[17] Moreover, Mg^{2+} deficiency–induced an elevation of circulating interferon-γ, which was blocked by SP (neurokinin-1) receptor antagonists.[13] In Mg^{2+}-deficient mice, plasma SP elevations occur during the first week along with increased SP receptor expression on T cells and heightened sensitivity to SP challenge, leading to enhanced cytokine production.[18] Concurrent SP receptor blockade *in vivo* attenuated superoxide generation by endogenously activated neutrophils.[19]

NEURONAL *N*-METHYL-*D*-ASPARTATE RECEPTOR AND EARLY NEUROPEPTIDE RELEASE

Stimulation of the *N*-methyl-D-aspartate (NMDA) receptor can result in neuropeptide release from C-fibers and the NMDA-associated channel can be blocked by extracellular Mg^{2+}.[20] Thus, we reasoned that hypomagnesemia could enhance Ca^{2+} stimulated opening of this channel. Specific NMDA receptor/channel blockers are available that can prevent hyperactivation of this complex. Dizocilpine (MK-801) is an NMDA receptor/channel blocker, which has been reported to prevent noise-mediated seizures[21] and to diminish the acoustic startle reflex[22] in Mg^{2+}-deficient rats. In our research, blockade of this receptor/channel with MK-801 prevented many proinflammatory changes, free radical production and cardiac apoptosis in Mg^{2+}-deficient animals.[23]

ROLE OF NEUTRAL ENDOPEPTIDASE WITH SUSTAINED SP ELEVATIONS IN MG^{2+} DEFICIENCY

During prolonged Mg^{2+} deficiency for up to 5 weeks, we observed persistent elevations of SP.[24] Although neuronal

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TABLE 1. Changes due to neurogenic inflammation in hypomagnesemia

Cardiovascular	Increased: Atrial and ventricular inflammatory cells (CD11b); apoptosis; peroxynitrite; protein oxidation; endotoxin receptor (CD14); substance P receptors; VEGF; ICAM-1; iNOS; superoxide; hydroxyl- and alkoxyl-radicals after ischemic/reperfusion of isolated heart, diastolic dysfunction
	Decreased: Neprilysin (NEP); myocardial contractility
Gastrointestinal	Increased: CD11b cell infiltrates; $CD14^+$ cells; intestinal permeability
	Decreased: NEP; intestinal villi epithelium
Central nervous system-neuronal	Increased: protein oxidation
	Decreased: Substance P
Blood	Increased: Substance P; CGRP; IL-1; IL-6; TNF-α; IFN-γ; endotoxin; thromboxane A_2; PGE_2; SP receptors on WBCs; malondialdehyde; NO- products; histamine; endothelin; RBC crenation; leukocytes; PMN leukocyte superoxide; oxidized glutathione (GSSG); triglycerides
	Decreased: RBC glutathione; Mg; PMN-NEP activity

VEGF, vascular endothelial growth factor; ICAM-1, intercellular adhesion Molecule 1; iNOS, inducible nitric oxide synthase; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; PMN, polymorphonuclear.

release of SP occurred often within the first week, other mechanisms (eg, new synthesis) may contribute to sustained SP levels.[25] We also suspected that the degradation of SP by peptidases might be impaired during Mg^{2+} deficiency; so, we focused on neprilysin (NEP) activity in Mg^{2+}-deficient rats. NEP is a principal SP-degrading enzyme,[26] but other peptidases (angiotensin converting enzyme, di-peptidyl amino peptidase IV, aminopeptidase M) may also degrade SP to a lesser extent.[27] NEP is expressed by various tissues and cells, including heart, small intestine, kidney, brain, airway epithelium, vascular endothelium,[28] neutrophils[29] and macrophages.[30] NEP inactivation may lead to enhanced SP-mediated systemic inflammation during Mg^{2+} deficiency. NEP is a target of oxidative damage: by-products of lipid peroxidation form covalent adducts through its histidine and lysine residues.[31] NEP oxidation may also be an age-related process, as implicated by decreased NEP levels in the brains of patients with Alzheimer's disease, where beta-amyloid, also a substrate of NEP, accumulates in brain tissue of these patients.[31,32] Because both lipid and protein oxidation occur during Mg^{2+} deficiency, we assessed the activity of NEP in neutrophils (PMNs), cardiac and intestinal tissues. We found a significant loss of NEP enzymatic activity in PMNs isolated after 3 weeks of Mg^{2+} deficiency.[33] Using immunohistochemistry and Western blot techniques, we also found significant losses of NEP in cardiac and intestinal tissues from Mg^{2+}-deficient animals.[34] Thus, we concluded that part of the sustained elevations of SP in Mg^{2+} deficiency are due to impairment of NEP activity by a combined a reactive oxygen species and reactive nitrogen species insult.

INTESTINAL PERMEABILITY IN CHRONIC MG^{2+} DEFICIENCY

The intestines also contain neuropeptides,[35] and they may be another source of elevated plasma SP. After 1 week of Mg deficiency, mucosal inflammation was evident and pronounced leukocyte infiltration occurred by 3 weeks, when significant decreases in mucosal barrier function were observed.[36] In the intestines, nitric oxide is generated from constitutive nitric oxide synthase to regulate vascular tone and endothelial permeability. In our studies,[37] increased NO products were observed with progressive hypomagnesemia and L-NAME prevented the subsequent gut inflammation. Enhanced gut permeability is considered an initiating factor in the development of several diseases, including diabetes, celiac and inflammatory bowel diseases, emphasizing the importance of maintaining mucosal barrier integrity.[38]

ENDOTOXEMIA AND CYTOKINE STIMULATION

Endotoxin (lipopolysaccharide [LPS]) is known to induce systemic elevation of tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and IL-6, which may contribute to chronic cardiac dysfunction.[39] LPS stimulates cytokine secretions from macrophages, and SP-treatment of macrophages also enhances cytokine secretion.[40] LPS can also stimulate secretion of TNF-α directly from adult rat cardiomyocytes.[41] Importantly, LPS-induced cytokine release depends on LPS binding to CD14 receptors on cardiomyocytes.[41] In hypomagnesemic rats, the substantial increases in plasma TNF-α, IL-1 and IL-6 may be due partly to endotoxemia. Indeed, we observed that *in vivo* SP receptor blockade in Mg^{2+}-deficient rats significantly lowered plasma TNF-α and endotoxin levels.[9,33] This suggests that both SP and endotoxemia may participate in TNF-α elevations, which may play a prominent role in chronic heart failure (CHF).[42] High TNF-α and CD14 levels were found in patients with CHF and circulating LPS was reported to be an important stimulus to TNF-α production in CHF.[42,43] TNF-α and IL-6 were also elevated in the plasma and myocardium of patients with end-stage heart failure.[44] Cardiac-specific overexpression of TNF-α also resulted in a heart failure phenotype in mice typified by LV dysfunction and remodeling.[45] In our 3- to 5-week Mg-deficient rats, TNF-α and endotoxin were markedly elevated[34] and may be major contributors to the cardiomyopathic contractile dysfunction.[24]

THE ROLE OF ENDOTOXIN RECEPTORS

Cellular receptors for LPS include CD14- and Toll-like receptors. LPS binds to the CD14 receptor, which mediates the production of inflammatory cytokines. The importance of CD14 receptor in the LPS-induced response was shown using transgenic mice over-expressing this receptor[46] and in CD14 receptor-deficient mice.[47] Molecular and immunological evidence showed CD14 receptor on cardiomyocytes and that the cardiodepressant effects of LPS were dependent on CD14 signaling.[41] In our Mg^{2+}-deficient rats, up-regulation of CD14 receptor was seen in both cardiac and intestinal tissues.[48] Thus, in the presence of enhanced gut permeability and increased CD14 receptor expression in the heart, endotoxin may have an amplified effect on the release of inflammatory cytokines that may further enhance cardiac inflammation.

CARDIAC DYSFUNCTION IN MG DEFICIENCY

Overall, our observations that a SP receptor blocker decreased both endotoxin[33] and TNF-α[9,11] levels suggest a

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