Stress and Magnesium with Special Regard to the Gastrointestinal Tract

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Guest Lecture*

Zusammenfassung

In Abhängigkeit von Schweregrad und Dauer kann ein Mg-Mangel einmal als Stressor wirken und verschiedene Stadien des Generellen Adoptions-Syndroms auslösen — oder als konditionierender, klinisch „stummer" Faktor, der die Sensivität gegenüber plötzlich einwirkendem Stress erhöht. Daten, die an Labortieren, isolierten Organpräparaten und auch an Menschen erhoben wurden, belegen diese Aussage.
Magnesiumgaben hemmen nicht nur die genannten unerwünschten Reaktionen, sondern können auch nachweislich günstige Effekte auslösen, ohne daß ein Mg-Mangel besteht. Der Gastrointestinaltrakt reagiert sehr empfindlich auf Schwankungen der extrazellulären Mg-Konzentration. Klinische Aspekte werden diskutiert.

Summary

Depending on its severity and duration, Mg deficiency may act as a stressor-eliciting different stages of the general adoptation syndrome — or as a conditioning factor, sensitizing the organism against acute exposure to stress. Data gained in intact laboratory animals, isolated organ preparations and in man support this view. Mg supplementation not only attenuates these adverse reactions but can also exerts beneficial effects in the absence of an over Mg deficit. The gastrointestinal tract reacts very susceptible to fluctuations of extracellular Mg concentrations. Clinical implications are discussed.

Résumé

Selon sa sévérité et sa durée, une carence en magnésium peut agir comme un facteur de stress — suscitant divers stades du syndrome d'adaptation générale — ou agir comme facteur de conditionnement «silencieux», sensibilisant ainsi l'organisme aux stress violents. Les résultats obtenus en laboratoire sur des préparations isolées d'organes, ainsi que chez des animaux d'expérience intacts et chez l'homme confirment ces données. Un supplémentation magnésienne atténue non seulement ces manifestations indésirables mais peut également exercer des effets bénéfiques, en l'absence d'une carence en Mg. Les voies digestives sont particulièrement sensibles aux fluctuations des concentrations extra-cellulaires de Mg. On discute des implications cliniques.

Stress, conditioning factors and disease

Chronic exposure to stressors is known to elicit the General Adaptation Syndrome (GAS) passing through the following three stages (*Selye*, 1976): Stage I: Alarm Reaction, Stage II: Resistance, Stage III: Exhaustion. Stages I and III are characterized by decreased resistance against all kinds of stimuli; acute gastroduodenal peptic ulcers or bleeding surface erosions can often be observed together with an atrophy of the lymph nodes and the thymus gland and an enlargement of the adrenals (stress triad). During Stage II on the other hand, the organism has become adapted to the causative and in addition to quite different stressors, a phenomenon called cross-resistance and being the theoretical basis of all active rehabilitation measures. Thus, the GAS is the sum of all nonspecific, systemic reactions of the body that occur upon continued exposure to stress.

The question, why the same degree of stress may produce quite different lesions in different individuals and even different organs can only be answered when the so-called "conditioning factors" are also taken into account. These factors which may be endogenous (genetic predisposition, age, sex) or exogenous (dietary factors, climate, certain hormones and drugs) usually do not produce overt clinical symptoms; however under their influence a normally well tolerated degree of stress can become pathogenic and can cause diseases of adaptation. This situation is comparable to a chain subjected to mechanical tension: that particular link will break first that has become weakest as a result of conditioning factors (*Selye*, 1976).

Magnesium (Mg) certainly plays an important role within the GAS, i.e. within the pathogenesis of diverse diseases of adaptation. Theoretically, a deficit (which may develop acute or chronically, with different degrees of severity, persisting during shorter or longer periods of time) may act as a **stressor** eliciting an Alarm Reaction and even other Stages of the GAS (*Heroux* et al., 1977) or as a **conditioning factor** sensitizing certain organs against different kinds of stressors. As a stressor Mg depletion should evoke hormonal changes or other adverse biological responses typical for known somatic stressors (traumatic injury, excessive muscular work, toxic amounts of drugs a.s.o.) or psychological/psychosocial oversti-

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mulation (noise, pain, isolation, crowding, frustration, fear, joy a.s.o.). As a conditioning factor, however, a Mg deficit should remain clinically quiescent, resp. latent, for longer periods of time and should induce pathologic reactions only in combination with unexpected strong stress reactions. In both cases the correction of the deficit by adequate supplementation should improve health.

Mg depletion as a stressor

Neurologic and gastrointestinal signs predominate when severe Mg depletion is induced: anorexia, nausea, weakness, lethargy, staggering and loss of body weight are typical symptoms together with hyperirritability or hyperexcitability; later tremor, tonic-clonic seizures, convulsions and opisthotonus occur and mortality increases. This is true for laboratory animals (*Kruse* et al., 1932), ruminants (*Sjolemma* et al., 1932) and also for man (*Shils*, 1969, *Paunier* et al., 1965). Although severe hypomagnesemia is generally present, clinical symptoms correspond better to (lowered) cerebrospinal fluid Mg (*Scholz*, 1981). Brain Mg however, is only slightliy decreased by a maximum of –10 % to –15 % (*Chutkow*, 1981). Concerning the gastrointestinal symptoms it should be noted that in rats — under these conditions — the appearance of gastric peptic ulcers and erosions has been described in addition to thymolymphatic involution (*Classen*, 1981 a) which are both typical stress-induced lesions, and that the small intestine transit time is increased (*Landin* et al., 1979).

Except severe organic lesions, all symptoms listed above usually disappear rather quickly when sufficient amounts of Mg are supplemented. It must however be emphazized that severe Mg depletion evoking a typical Alarm Reaction will develop very rarely under clinical conditions in man. Hence, Mg deficiency is more likely to play an important role as a conditioning factor.

Mg deficiency as a conditioning, Mg supplementation as a stress-protecting factor

Several strategies have been successfully employed to demonstrate that even a moderate degree of Mg deficiency may markedly aggravate diverse stressor effects. Conclusive arguments are **1.** a biochemically proven, pre-existing Mg deficit and **2.** a significant attenuation of acute stress reactions after the correction of the deficit by adequate Mg supplementation.

In intact laboratory animals these relations are proven using different stressors and studying several target organs: Early observations concern the grossly impeded physical development and well-being of whole animals at rapid growth (*Kruse* et al., 1932, *Scholz*, 1981). The development of cardiac necroses and arrhythmias is facilitated on exposure to exogeneous catecholamines or to immobilization (*Seelig*, 1980, *Lehr*, 1981, *Vormann* et al., 1983, *Classen* et al., 1987 a), to cold (*Heroux* et al., 1977) or to noise (together with inner ear damage (*Ising* et al., 1982, *Joachims* et al., 1983). Other target organs are (impaired) functions of the gastro-intestinal tract (*Landin* et al., 1979) the gastric mucosa (appearance of erosions and peptic ulcers)(*Classen* et al., 1981, 1985, 1986), (impaired) responses of the immunsystem to specific stimuli (*Larvor*, 1980) or reduced muscular performance (*Hirneth* et al., 1987). In many of these studies increased levels of stress hormones (mostly catecholamines) have been measured. — Alternatively, the effects of stress hormones and drugs have been studied at different Mg concentrations using **isolated organs or organ preparations**: At lowered extracellular Mg concentrations the effects of vasoconstrictors are generally enhanced (*Altura* et al., 1986, *Nguyen Dong*, 1985) as well as the effects of agonists on other smooth muscles like tracheal or gastrointestinal tissue (*Classen* et al., 1988, 1989) or the response of the Langendorff heart to stimuli (*Döring*, 1989). Since these increased, or pathologic responses normalize and finally disappear at increasing extracellular Mg concentrations, and can also be achieved by increasing extracellular Ca levels, Mg has been called the "physiologic calcium antagonist". — **In man**, too, increased sensitivity to stressors has been described in the presence of a proven (though usually less pronounced) Mg deficit: Mental stress resistance is decreased (*Durlach*, 1988) and the development of a tetanic syndrome (*Durlach*, 1988, *Fehlinger*, 1988) and of spastic-functional disorders in children is facilitated (*Classen, O.* et al., 1986, *Schimatschek* et al., 1989). Other examples are: decreased resistance to the stress of pregnancy (*Spätling* et al., 1988), to premenstrual tension (*Abraham*, 1982), to noise (*Joachims* et al., 1987) or to vasoactive transmitters (*Fehlinger* et al., 1984).

It is quite logical and easy to understand that under these conditions symptoms disappear and stress resistance increases after the correction of the Mg deficit. However, **beneficial effects of extra-Mg** have also been observed in the absence of a pre-existing Mg deficit. In most cases the monomagnesium-L-aspartate hydrochloride (MAH, Verla, Pharm, Tutzing/FRG) was used as Mg salt being well available on oral administration without affecting the acid-base-metabolism (*Classen* et al., 1987). With regard to **animals** significant cardioprotection has been achieved in rats (*Vormann* et al., 1983), pigs, piglets (*Schumm*, 1984) or broilers (*Grashorn* et al., 1988) subjected to toxic doses of adrenaline, to transportation stress or to the stress of rapid growth. In pigs the occurrence of PSE-meat is inhibited (*Schumm*, 1984) as well as cannibalism and secondary sterility of sows (*Niemack* et al., 1979). Furthermore it has been shown in rats that extra-Mg inhibits the stress-induced release of catecholamines and of corticosterone as well as the development of stress ulcers (*Classen* et al.,

1986, 1985). At least in young laboratory animals extra-Mg significantly increases bone-Mg which serves as a mobilizable reservoir (*Günther*, 1986). Thus Mg-loading significantly increased the latency until the appearance of clinical symptoms of Mf deficiency in rats fed deficient diets (*Classen* et al., 1988). — Beneficial effects of extra-Mg have also been shown **in man** without a proven, pre-existing Mg deficit. Probably, in these cases, too, increased bone-Mg buffers blood-Mg which tends to decrease following acute stress reactions (*Ising* et al., 1982). Alternatively, Ca-antagonistic effects of increased Mg levels have to be taken into account. Thus, beneficial effects of extra-Mg have been described in adults (*Fehlinger*, 1980) or children (*Ducroux*, 1984) suffering from the tetanic syndrome, in patients with cardiac dysrhythmia (*Iseri*, 1986), variant angina (*Cohen* et al., 1984) or acute myocardial infarction (*Morton* et al., 1984, *Rasmussen* et al., 1986, *Smith* et al., 1986). Additional indications are (methacholine-induced) bronchoconstriction (*Rolla* et al., 1987), pre-eclampsia resp. eclampsia (*Sibai*, 1982, *Conradt* et al., 1984), stress-induced hypertension (*Rüddel* et al.: 1988), liberation of stress hormones (*James*, 1985, *Golf* et al., 1984) or of intracellular proteins during prolonged muscular exercise (*Bertschat* et al., 1986). Under special conditions, MAH (*Weiss* et al., 1986) is even superior to synthetic Ca antagonistis (*Classen* et al., 1985, *McGrath* et al., 1984) perhaps because of weak tranquillizing effects (*Krämer* et al., 1979).

Magnesium and the gastrointestinal tract

As mentioned already, Mg deficiency aggravates, and supplementation attenuates some stress reactions of the GI-tract. However, in contrast to blood vessels, corresponding systemic studies on these tissues have so far not been performed. — We did not detect significant effects when tissues of Mg-depleted rats were studied (in contrast to *Landin* et al., 1979). However, lowering of extra-cellular Mg significantly potentiated agonistic effects (*Classen* et al., 1988). Using MAH as Mg salt and rats as test animals, the following effective inhibitory concentrations were determined (mmol Mg/l of Tyrode solution): amplitude of spontaneous contractions of the jejunum; .0.8; spontaneous, frequency of contractions (Ileum): 8.9. The EC_{50} concentrations of electrically stimulated tissues amounted to (mmol Mg/l): cranial, resp. caudal **oesophagus** 7.6 and 5.6; **stomach** (florestomach and corpus) 1.6 and 0.8; **duodenum** 1.3; **jejunum** 0.8; **ileum** 1.5; **cecum** 1.5 to 2.5; **colon** ca 1.0. In addition, 50 % relaxation was offered against EC_{50} concentrations of the following transmitters; acetylcholine 1.7; histamine 1.5; serotonin 1.9; prostaglandin D_2 1.8 and prostaglandin F_2 alpha 2.9 mmol Mg/l (isolated rat ileum).

In conclusion Mg deficiency not only sensitizes isolated organs, respectively the whole intact organism against adrenergic overstimulation (*Speich* et al., 1980), but also against vagal stimuli and transmitters affecting the motility of the GI-tract. The Mg concentrations needed for 50 % inhibition are remarkably low and correspond to those used traditionally in physiologic solution, e.g. of *Sund, Tyrode* or *Krebs-Henseleit.* These data may help to explain the high frequency of stomach-ache in children with marginal Mg deficiency (*Schimatschek* et al., 1989) and the beneficial effects of Mg supplements not only in these patients, but generally in patients with GI-disorders (although in internal medicine Mg is usually prescribed as an antacid).

Since Mg plays a central role within the pathogenesis of stress-related disease and may also act as a physiologic Ca antagonist special attention should be paid to keep its supply optimal, to correct losses immediately, or better to prevent them prophylactically.

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