Magnesium and Stress

Subjects: Nutrition
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Definition

Magnesium deficiency and stress are both common conditions among the general population, which, over time, can increase the risk of health consequences. Clinical and pre-clinical evidence suggest that stress could increase magnesium loss, causing a deficiency; and in turn, magnesium deficiency could enhance the body's susceptibility to stress, resulting in a magnesium and stress vicious circle.

1. Introduction

Stress and magnesium deficiency are common health conditions among the general population[1][2]. Interestingly, clinical symptoms of magnesium deficiency and stress are very similar, notably fatigue, anxiety, irritability, nervousness, muscle cramps, gastrointestinal spasms and headache [3][4]. Of note, low magnesium status has been associated with stressful conditions, and conversely, chronic exposure to stressful stimuli results in magnesium loss [5]. This bidirectional cause-effect relationship between magnesium and stress was first described in the early 1990s [5][6] and referred to as the vicious circle. Nowadays, considerable pre-clinical and clinical evidence support the beneficial effect of magnesium supplementation in different types of stress.

2. Magnesium: biological role and homeostasis

Magnesium is an essential micronutrient for humans [7] involved in almost all major metabolic and biochemical processes (**Figure 1**), and acting as a cofactor in hundreds of enzymatic reactions [8]. About 50–60% of body magnesium is stored in the bones, with the remainder distributed in soft tissues such as muscles [9][10] and the brain [11][12]. Only 1% of the total magnesium is extracellular and 0.3% of this circulates in serum [13]. In clinical practice, normal serum magnesium values are considered to be within the 0.7–1.0 mmol/L range [14]. Magnesium deficiency is generally defined when serum concentrations drop below 0.7 mmol/L[15].

Magnesium homeostasis is tightly regulated and relies on the dynamic balance between intestinal absorption, kidney excretion and bone storage (**Figure 1**) [16]. However, chronic latent magnesium deficiency (serum levels <0.85 mmol/L) may occur despite normal magnesium levels in serum and remain undetected (non-specific symptoms) with a potential long-term impact on health [7][17].

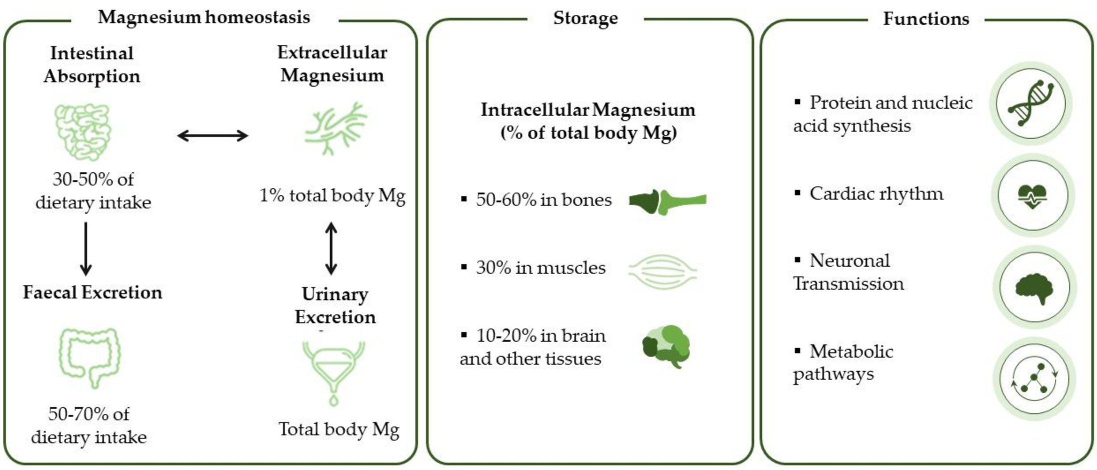

Figure 1. Magnesium homeostasis. Figure adapted from Jahnen-Dechent, 2012 [17].

Among the factors contributing to magnesium deficiency (e.g. lifestyle; some medicines; pathological conditions), clinical evidence also suggest that chronic stress may cause magnesium loss [18][19][20][21]. A recent study found that nearly half (~44%) of the subjects screened for stress had chronic latent magnesium deficiency [22].

In addition, multiple studies have consistently shown that the dietary intake of magnesium is often inadequate and does not reach the recommended dietary allowances (**Table 1**) [3][23][24][25] across different countries worldwide [26][27][28]. This trend is further increased by the consumption of processed food typical of Western diets, with magnesium being depleted by up to 80–90% [3][15].

Table 1. Current magnesium recommended daily allowance across countries.

Country	Magnesium, mg/day	
	Men	Women
Italy [29]	240	240
Russia [30]	300	300
Japan [31]	320–340	220–230
Poland [32]	400–420	310–320
USA and Canada [33]	400–420	310–320
France [34]	420	360

Values shown refer to adult population only (≥19 years).

3. Stress and interaction with magnesium status

Stress is considered as an ongoing and adaptive system that enables an individual to assess, cope and predict constantly changing conditions. However, the capacity of this stress system is limited and can be overloaded, resulting in poor health outcomes, particularly those related to mental illness like depression or cognitive deficits [35]. The hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system, comprising of sympathetic nervous system (SNS) and parasympathetic nervous system (PSN), have been identified as the mediators of the so-called “neurobiological stress model” [36][37][38]. In this model, important mediators like catecholamines (released from the sympathetic nerves and the adrenal medulla), together with the glucocorticoids (mainly cortisol, released from the adrenal cortex) regulate the stress response [36][37]. Cortisol also interacts with the serotonergic pathway and modulates the release of serotonin (5-hydroxytryptamine or 5-HT) neurotransmitter in response to acute or chronic stressors [39]. In addition to the regulation through feedback mechanisms, the HPA axis is also modulated by other central systems, particularly by the inhibitory action of the γ-aminobutyric acid (GABA), and the excitatory effect of glutamate [40].

The generalized unsafety theory of stress (GUTS) is a new psychological and cognitive theoretical model proposed by Brosschot in 2016 [41] that revises and expands the stress theory. Based on neurobiological and evolutionary evidence, GUTS hypothesizes that stressors are not necessary for a chronic stress response to occur but the perception of an unsafe state is enough. In GUTS, PNS is the key system controlling the stress response (particularly the vagus nerve and the prefrontal cortex activity) [41]

Of note, magnesium interacts with all the stress mediators mentioned above[11][42][43][44] overall serving an inhibitory function in the regulation and central neurotransmission of the stress response (neurobiological model), or by modulating the autonomic nervous system (GUTS model) [45][46][47]

Comprehensively, both pre-clinical and clinical studies’ results point to the bi-directional relationship between magnesium levels and stress: magnesium deficiency can induce symptoms and increase susceptibility to stress, and acute and chronic stress can precipitate magnesium deficiency. Summary of the preclinical and clinical evidence are shown in **Tables 2** and **3**, respectively.

Table 2. Summary of the pre-clinical and clinical evidence supporting the impact of stress on magnesium homeostasis.

Evidence of the impact of stress on magnesium homeostasis			
	Population tested	**Stress stimulus**	**Impact on magnesium**
Pre-clinical	Cats (N=30)	Withdrawal of blood; infusion of catecholamines ; potassium poisoning	↑Blood Mg [48]
	Guinea pigs (41)	Noise	↑Serum Mg, ↓Erythrocytes Mg [49]
	Rats (88)	Noise	↑Serum Mg, ↓Erythrocytes Mg [50]
	Rats	Noise	↓Serum Mg, ↓Erythrocytes Mg [51]
	Dogs	Physical exercise, temperature	↓Serum Mg [52]
	Rats	Ethanol/Restraint stress	↓Serum Mg [53]
	Rats	Cold	↓ Tissue content of Mg [54]
	Sheep	Dietary Mg restriction, cold	↓Plasma Mg [55]
Clinical	Adults (N=8)	Adrenaline infusion	↓Plasma Mg [56]
	Young adults (N=35)	Chronic or sub-chronic psychological stress	↓Plasma Mg [18]
	Healthy men (N=16)	Chronic sleep deprivation	↓Erythrocyte Mg [19]
	Young adults (N=35)	University exams	↑Urinary Mg [20]
	Young adults (N=30)	University exams	↓Erythrocyte Mg [21]

	Young adults (N=25)	Noise	↑Urinary Mg ↑Serum Mg [57]
	Healthy men (56)	Noise	↑Serum Mg, ↓Erythrocytes Mg; ↑Urinary Mg [58]
	Healthy men	Short- and long-term physical exercise	↑Plasma Mg [59]

Mg, magnesium.

Table 3. Summary of the pre-clinical and clinical evidence supporting magnesium status on stress susceptibility.[a] Only symptoms shown in ≥70% of women at baseline are reported.

Evidence of the impact of magnesium status on stress susceptibility

	Population tested	**Mg status**	**Stress stimulus**	**Impact on stress mediator/ stress**
Pre-clinical	Rats (N=84)	Mg-deficient	Noise	↑Catecholamines (NA, adrenaline, dopamine) [60]
	Mice (N=120)	Mg-deficient	Genetic selection	↑NA [61]
	Mice (N=80)	Mg-deficient	Genetic selection; forced swimming test; four-plate test	↑NA [62]
	Mice (N=100)	Mg-deficient	Genetic selection; immobilization test	↑Gastric ulcers [63]
	Mice (N=20/test)	Dietary Mg restriction	Hyperthermia; open field test; light/dark test; hyponeophagia test	↑CRH; ↑ACHT [64]
	Mice	Mg-deficient	Light dark test	Depression-like behaviour [64][65]
	Rats	Dietary Mg restriction	Forced swimming test	Depression-like behaviour [66][67]

	Rats	Dietary Mg restriction	Open field test	Stress/anxiety [66][67]
Clinical	Women (N=100)	Mg-deficient	-	Chronic emotional stress; irritability; fatigue; sleep disturbance; headache[a] [68]
	Adults (N=264)	Mg-deficient	-	Severe stress [22]
	Adults (N=100)	Mg-deficient	Poor sleep quality	↑CRP [69]
	Adults (N=109)	Mg-deficient	-	Depression/anxiety [70]

ACHTH, adrenocorticotropic hormone; CRH, corticotrophin-releasing hormone; CRP, C-reactive protein; Mg, magnesium; NA, noradrenaline.

Noteworthy, magnesium supplementation has proven beneficial effects for the treatment of symptoms of psychological daily stress (fatigue, irritability, sleep) [68], magnesium may reduce serum cortisol levels[71], and improve stress relief in people with severe stress [72].

4. Proposed model for the vicious circle of stress and magnesium deficiency

In summary, magnesium acts on several key physiological steps involved in the response to stressful stimuli, and also exerts long-term neuroprotective and anti-oxidant effects against stress

- Magnesium and HPA. *5-HT transmission:* Magnesium directly enhances the interaction between 5-HT and its membrane receptor [36], and is also an important cofactor in the synthesis of 5-HT[36]. *Glutamatergic transmission:* Magnesium inhibits the glutamate directly and indirectly by blocking the glutamate N-methyl-D-aspartate (NMDA) receptor and by enhancing its reuptake in the synaptic vesicles [65]. *GABA transmission:* A GABA-agonistic activity of magnesium has been observed, although the mechanism has not yet been elucidated [65]. *Cortisol:* Magnesium indirectly reduces the release of ACTH, therefore decreasing cortisol levels[65].
- Magnesium and neuroprotection. Studies have shown positive impact of magnesium on the expression of brain-derived neurotrophic factor, a growth factor involved in neural development and activity [73][74].
- Magnesium and oxidative stress. Magnesium may be involved in suppressing the production of free radicals in various tissues including the brain [11].

In response to a stressful stimulus, stress hormones are released causing an increase of magnesium extracellular levels[36]. As a consequence, higher magnesium concentrations are excreted through the kidneys [57]. When the stressor persists over time, this mechanism may contribute to magnesium (intracellular) depletion and deficiency [56][65], and trigger the stress and magnesium vicious circle as illustrated in **Figure 2**.

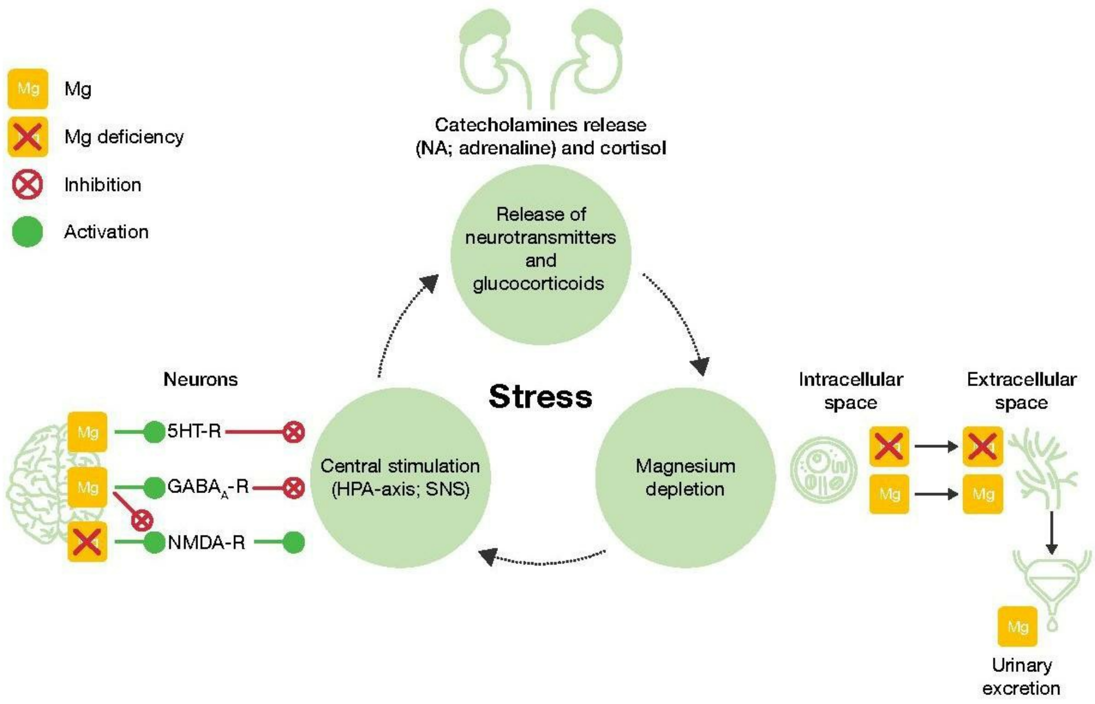

Figure 2. The vicious circle of stress and magnesium. GABAA-R, γ-aminobutyric acid-A receptor; Mg, magnesium; NMDA-R, N-methyl-D-aspartate receptor; NA, noradrenaline; SNS, sympathetic nervous system, 5HT-R, 5-hydroxytryptamine receptor.

5. Conclusion

To conclude, while there is good evidence from animal and human studies of the bi-directional link between magnesium and stress, further research is needed to better understand the impact of this correlation and the benefit of magnesium supplementation on general health. This research is fundamental to further support adequate magnesium dietary needs, particularly in the stressed population.

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Keywords

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