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REVIEW

## The Effects of Nutrients on Stress and Aggression: Integrative Approaches to Behavioral and Emotional Modification

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### ABSTRACT

As research on the interplay of nutrition and mental health evolves, “nutritional medicine” is attracting new enthusiasm from clinicians across a broad range of clinical subspecialties. In this review, we describe potential relevance of 6 nutrients in particular — Vitamin A, Vitamin C, Zinc, Magnesium, L-tryptophan, and Omega-3 fatty acids — on reducing or preventing the target symptoms of stress and aggression. Briefly: (1) Vitamin A may reduce the physical symptoms of stress, including inflammation, while (2) Vitamin C may reduce

psychological distress and attenuate acute mammalian stress-response; stress may (3) increase the body’s demand for Mg and exacerbate Mg deficiency, while Mg deficiency itself may increase vulnerability under particular stressors; (4) Zinc deficiency appears to correlate with psychological adaptive potential; (5) Omega-3 fatty acids may mitigate aggression and anger for stressed mammals. Tryptophan (6) depletion, finally, appears to correlate with increased aggression. Broadly speaking, as the literature evolves, there increasingly appears to be meaningful correlations between these nutrients and stress and aggression that justifies a call for further research.

**Key words:** Nutrition; Integrative medicine; Mental health; Stress; aggression; Vitamin A; Vitamin C; Zinc; Magnesium; L-tryptophan; Omega-3 fatty acids

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### INTRODUCTION

Recently, there has been a resurgence of interest in “nutritional medicine” and the impact of orally absorbed nutrients on mental health. In this literature review, we summarize recent research on select vitamins, minerals, and supplements that may prevent or mitigate the target symptoms of ego-dystonic stress and/or aggression. In particular, we focus on Vitamin A, Vitamin C, Zinc, Magnesium, L-tryptophan, and Omega-3 Fatty Acids in the context of the evolving literature on stress and aggression.

### VITAMIN A

While popularly known for its presumptive roles in promoting healthy vision, Vitamin A may also play critical roles in immune function, reproduction, cellular communication, and organ maintenance<sup>[1]</sup>. More recently, an evolving body of evidence suggests that that Vitamin A may play a role in stress-resistance.

Studies have shown that stress-resistance can be severely impaired in nutrient-deficient animals. Reduced resistance to cold has been reported in rats with pyridoxine, riboflavin, and Vitamin A deficiencies, for example. One study measured the effect of graded doses of Vitamin A on the resistance of rats to low ambient temperatures and x-irradiation injury. Rat litters were placed on a diet low in Vitamin A but enriched or supplemented with thiamine, riboflavin, pyridoxine, calcium pantothenate, nicotinic acid, ascorbic acid, biotin, folic acid, Vitamin B12, Vitamin D, and alpha-tocopherol acetate to produce subjects primarily deficient in Vitamin A.

The subjects were subsequently divided into groups and given oral supplements of Vitamin A for an average daily intake of 0, 2.5, 5, 10, and 50 USP units for groups I-V respectively. When group I rats became depleted of Vitamin A, half the rats in each group were placed in a refrigerator to induce physiologic stress. The rats given 2.5 USP units or more of Vitamin A survived at room temperature, but only those given 5 USP units or more showed substantive adjustment to cold. In another study, one somewhat more difficult to generalize into human correlates, increased Vitamin A doses demonstrated a significant positive correlation with the percentage of rats that survived the single exposure to x-irradiation. *The authors suggested the results of the study implied that doses of Vitamin A sufficient for survival and good growth are not enough for effective physical stress resistance*<sup>[2]</sup>.

Another study of rodents found that in groups injected with Vitamin A after physical restraint, the formation of stress ulcers caused by restraint stress was significantly reduced compared to the control group. Though the supplementation did not completely prevent ulcers from forming, the ulcers formed were fewer and smaller among the cohort super-dosed with Vitamin A. Gastric ulcers have been hypothesized to be related to physiological stressors, in some instances, leading one to consider the possibility that *Vitamin A may reduce the physiological effects of stress*<sup>[3]</sup>.

Across a wide range of therapies for humans, awareness of physical/psychological “stress” alone has been coupled to the important concept of physical and psychological “resilience.” Vitamin A has been shown to introduce a degree of resilience during wound healing. In one study of rats subjected to moderately severe injury, those supplemented with Vitamin A demonstrated decreased thymic involution and delayed or prevented adrenal hypertrophy. The Vitamin A supplementation also produced enhanced migration of white blood cells directly to the sites of physical injury, in theory enhancing wound healing<sup>[4]</sup>. This response reduced inflammation. Since chronic stress of many kinds appears to be related to increased inflammation, the results suggest that Vitamin A may attenuate maladaptive and harmful consequences of stress.

## VITAMIN C

Vitamin C is classically involved in protein metabolism and the biosynthesis of collagen, L-carnitine, and some neurotransmitters<sup>[5]</sup>. A robust and diverse body of research is evolving that suggests Vitamin C may also play a substantive role in mood and stress levels.

In Wang *et al.*'s 2013 study of the effect of Vitamin C versus Vitamin D supplementation on the mood of acutely ill (hospitalized) patients, a cohort of individuals who presented with Vitamin C depletion were given Vitamin C. This cohort demonstrated a 71% decrease in mood disturbance and a 51% decrease in psychological distress. Vitamin D had insignificant effects. Though the study was small, similar clinical trials of Vitamin C have shown statistically significant improvements in mood. One caveat, among several, bears special mention: Supplementation, in this study, was primarily done on

subjects deficient in Vitamin C; one thus cannot conclude that these and similar results show the effects of Vitamin C supplementation on individuals with normal plasma levels of Vitamin C<sup>[6]</sup>.

However, the potential role in stress-response biochemical at the convergence of so-called psychological and physiologic models is striking: Evidence suggests that in stressful situations, the ascorbic acid content of the adrenal glands decreases, increasing the need for Vitamin C intake, while ascorbic acid utilization by the adrenal glands may increase during stress or illness<sup>[7]</sup>. Pathways mechanistically effecting any number of the Endocrine physiologic axis are natural nodes of potential convergence with both so-called “psychologic” and “physiologic” stress, and invite further awareness of potential effects on affective or mood states.

Some animal studies have suggested that ascorbic acid supplementation may reduce stress-induced cortisol release and other indicators of psychological stress<sup>[8-11]</sup>. To test this in humans, one study examined the effect of high dose sustained-release ascorbic acid on measures of stress, including systolic blood pressure, diastolic blood pressure and subjective stress units calculated from the Trier Social Stress Test. Subjects began the study with normal plasma ascorbic acid levels. Individuals who had taken ascorbic acid supplements in the 14 days prior had significantly lower systolic blood pressure immediately before and after the TSST. The mean systolic blood pressure of the ascorbic acid group returned to pre-stress levels within 10 minutes after the TSST, while it took 40 minutes for the placebo group to do the same. Plasma ascorbic acid level was associated with less systolic blood pressure stress reactivity, less diastolic blood pressure reactivity, and less subjective stress reactivity. However, there was no statistically significant difference between the reduction of stress of the two groups over the 14 day interim. This data, the authors argue, suggests that Vitamin C supplementation may be more effective for immediate stress, or anxiety, rather than general long-term stress<sup>[12]</sup>.

## MAGNESIUM

Magnesium has classically been thought to play important roles in biochemical reactions responsible for protein synthesis, muscle and nerve function, energy production, blood glucose control, and blood pressure regulation<sup>[13]</sup>. Additionally, various processes related to magnesium, some inter-related to the aforementioned roles, may influence sensitivity to and expression of stress.

Studies have shown that stress causes intracellular loss of magnesium with subsequent increased magnesium excretion.<sup>[14]</sup> So-called “Type A” personalities, differently defined but sometimes understood as personalities that demonstrate a proclivity to competitiveness, aggression, and impatience, among other traits, appear to be more susceptible to extreme stress when compared to so-called “Type B” personalities (sometimes characterized as psychologic phenotypes that are more likely to demonstrate tolerance and patience in stressful situations). One study measured the RBC and plasma concentration of Mg before and after a stressful event for generally healthy Type A and Type B subjects. The Type A group demonstrated an increase in plasma Mg and a decrease in RBC Mg, which is consistent with the findings that stress may cause intracellular magnesium loss. Type A subjects, it has been hypothesized, may thus tend toward hypomagnesemia<sup>[15,16]</sup>. Hypomagnesemia may in turn enhance the effects of stress, as shown by a study of Mg-deficient rats under noise stress<sup>[17,18]</sup>. Chronic Mg deficiency has been associated with hyperexcitability of the nervous system, and therefore an increased sensitivity to stress<sup>[19,20]</sup>.

As well as stress sensitivity, adverse effects of stress on the cardio-

vascular system are increased by magnesium deficiency. Catecholamine and corticosteroid excess cause Mg loss and inactivation. Though magnesium deficiency is uncommon in developed nations, high intakes of fat or calcium can contribute to magnesium inadequacy. Interestingly, a high Ca/Mg ratio has numerous negative cardiovascular effects, including platelet aggregation, blood coagulation, and vasoconstriction. Both physical and emotional stress increase the body's requirement for magnesium<sup>[14]</sup>. Less catecholamine is released in high Mg solutions, while Ca has the opposite effect<sup>[20-24]</sup>. Emotional stress also increases corticosteroid release in rats<sup>[25]</sup>. In runners, Mg supplementation decreased CS and catecholamine excretion<sup>[26]</sup>. Two studies have demonstrated that epinephrine infusions reduce plasma Mg in healthy subjects<sup>[27,28]</sup>.

Stress can also cause an increased functional deficiency of magnesium. MCS hormones affect the absorption of Mg and increase urinary Mg excretion in animals and individuals with hyperaldosteronism induced by adrenal tumors<sup>[29-32]</sup>. Stress also increases serum free fatty acids, which bind and inactivate Mg in the blood and heart, increasing functional deficiency of Mg. Stress and increased serum FFA levels are associated with decreased serum Mg<sup>[33,34]</sup>. Among five trained runners and one untrained, there was an increase in mean FFA over the course of a marathon, corresponding with a decline in serum Mg except in the untrained runner, who had been supplemented with Mg<sup>[35]</sup>.

Personality also appears to influence the cardiovascular response to stress and Mg. Type A subjects have greater excretion of catecholamines than Type B subjects in response to the same noise and psychological stress, with the latter demonstrating higher blood Mg<sup>[16,36]</sup>. Durlach suggests that Mg deficiency increases vulnerability to stress and increases its harmful effects<sup>[37]</sup>. Stressed workers and students did not experience a rise in blood pressure with Mg supplementation of 6-7 mg/kg/day, while they did on 5 mg/kg/day, though both exceed the RDA<sup>[38]</sup>.

## ZINC

Zinc is important for immune function, protein synthesis, wound healing, DNA synthesis, cell division, and normal growth<sup>[39]</sup>. However, zinc may also be related to stress and cortisol levels.

Chen *et al.*'s 2006 study of rats determined that zinc deficiency may lower the body's adaptability to psychological stress. Restraint stress was induced in rats on zinc-deficient, normal, and zinc-supplemented diets. Zinc-deficient rats not under stress had significantly higher plasma cortisol levels than the controls, and stressed, zinc-deficient and stressed control rats had significantly higher cortisol levels than their stress-free counterparts. There was no significant difference between cortisol levels of zinc-supplemented stress and control groups, suggesting that higher levels of zinc may mitigate the effects of stress.

Additionally, metallothionein production has been shown to be up-regulated in stress zinc-deficient rodents while downregulated in their zinc-deficient counterparts. MT production was greater in all stress groups compared to their respective controls; although stressed, zinc-deficient rats had the highest cortisol levels, they did not have the highest MT production of the rodents in the three stressed groups. These results suggest that zinc levels can affect MT induction in the hippocampus and that zinc deficiency may lower adaptability to psychological stress<sup>[40]</sup>.

Not only may zinc lower adaptability to stress, but increased cortisol may be associated with lower zinc levels, due to increased excretion of zinc. In one study of twelve high performance male volleyball

players and twelve male university students, results showed that more strenuous exercise was positively associated with both excretion of Zn and levels of cortisol, implying a potential negative correlation between zinc and cortisol levels<sup>[41]</sup>.

Additionally, further research on the relationship between cortisol and zinc levels supports a negative association. Since some evidence shows that hypozincemia and hyperzincemia are associated with alterations in adrenal secretion<sup>[42,43]</sup>, one study determined the acute effect of zinc on cortisol levels. In this study, 27 normal individuals of both sexes aged 20-27 years were asked to fast for twelve hours. After blood was drawn for baseline levels, subjects were given either 0, 25.0, 37.5, or 50.0 mg of zinc. Blood samples were taken at 30 minute increments for 240 minutes or at 10 minute increments for 120 minutes. Absolute differences in serum concentration were calculated by subtracting the cortisol level at a given time from the basal plasma level of cortisol. Statistical analysis showed that the basal difference was significantly higher in the experimental group than the control at all times. The results suggested that high blood zinc levels can inhibit cortisol levels in normal individuals.

Though the sample size of this study was small, the results were statistically significant and suggest that zinc levels negatively correlate with cortisol levels. Since high levels of cortisol have been suspected to exacerbate stress and anxiety (as well as reflect heightened autonomic states of arousal), zinc supplementation may help reduce stress<sup>[44]</sup>.

## OMEGA-3

Omega-3 polyunsaturated fatty acids serve as important components of cell membranes and energy production<sup>[45]</sup>. Evidence for potential impact on modulation of aggression and anger also appears to be evolving.

One study of college students determined the preventative effect of DHA on aggression during stressful events. Students were divided into control and experimental groups and given either supplemental DHA capsules or control oil capsules for three months. The beginning of this period was characterized by low psychological stress time during summer vacation, while the end was characterized by high psychological stress time, exams. At the beginning and end of this period, the students took a psychological test to measure aggression (P-F Study). The control group's "extraggression," aggression against others, was significantly higher at the time of the second test, while there was no significant change in the DHA group. The authors suggest that DHA supplementation may thus prevent the increase of extraggression in times of mental stress<sup>[46]</sup>.

A study of substance abusers in a rehabilitation program tested the effect of n-3 polyunsaturated fatty acids (PUFAs) on anger levels, with the results showing a decrease in anger levels with n-3 PUFA supplementation. The dietary data showed an association between fish consumption and aggressive behaviors. There was a significant difference between daily fish intake of patients with a history of assaultive behavior and those without. In the study, subjects received either capsules containing 3 g of n-3 PUFAs or placebo capsules daily for three months. The PUFA group patients demonstrated a significant decrease in anger scores over the administration period, while the control group experienced no change. Some individuals were followed for an additional 3 months after the administration period and maintained decreased anger scores with no return to baseline. This study was limited by the small sample size, but it provides some evidence that increased Omega-3 consumption may reduce anger and aggression<sup>[47]</sup>.

## L-TRYPTOPHAN

L-tryptophan, an essential amino acid, has been known to have an important role in protein synthesis and several other metabolic processes, including serotonin synthesis<sup>[48]</sup>. It may also affect stress and aggression levels.

Cleare's 1995 study found that tryptophan depletion increased aggression rating scores. 24 male subjects selected due to high levels of trait aggression (> 40 on Buss-Durkee hostility inventory) were administered 100-g tryptophan-free amino acids, or amino acids with 10.3 g of tryptophan added. Tryptophan significantly decreased in the first group and increased in the second group. Subjects completed an aggression rating scale and a mood rating scale (both scored out of 100) before administration and 5 hours after ingestion. The tryptophan-depleted group had a significant increase in the variables "angry, aggressive, annoyed, quarrelsome, and hostile," with all of these showing a difference of 20 percentage points or more. "Discontent" showed a significant increase in the tryptophan-depleted group and a decrease in the tryptophan group. This study can be interpreted to suggest that tryptophan depletion corresponds with enhanced aggression in individuals with preexisting aggressive traits<sup>[49]</sup>.

Moeller et al's 1996 study of the effect of tryptophan depletion on aggression in healthy males demonstrated a significant increase in aggression after tryptophan depletion. Moeller's team suggests that the association between tryptophan levels and aggressive response may be due to tryptophan's role as a limiting reagent in the production of serotonin; hence, reducing tryptophan could reduce serotonin levels and increase aggression. In the study, ten subjects were given tryptophan-depleting amino acid mixtures of 25 g and 100 g doses after 24 hours of low-tryptophan diets. Aggressive response was measured by the Point Subtraction Aggression Paradigm (PSAP) in 6 intervals on each day of testing. In this test, the choice to subtract points from a fictitious partner reflected the aggressive response, as compared to the choice to augment one's own points. The stimulus for aggression was a randomized point subtraction from the subject's counter attributed to the partner. The first week after acclimation to the setup, the 25 g dose was given to each subject prior to the testing, followed by a baseline day before the week of the 100 g dose. Blood samples were taken before the administration of the drink and 5 hours after and plasma tryptophan was measured from these samples. The 100 g dose decreased plasma tryptophan to a significantly greater degree than did the 25 g dose. The 100 g dose produced a significant increase in aggressive responding 5 hours after the administration as compared to the same time on the baseline day, while the 25 g dose produced a statistically significant increase in aggressive responding from the baseline 6 hours after drink administration. These results suggest an association between tryptophan depletion and increased aggression<sup>[50]</sup>.

## CONCLUSION

There is a growing interest in the use of non-pharmacological approaches to stress and aggression. Aside from behavioral activation and lifestyle changes, orally absorbed vitamins, minerals, and supplements may have promise for the prevention and mitigation of some symptoms of critical relevance to psychiatric and psychological health and well-being. Much of the research to date on aggression has been on small mammals; future studies may involve the evaluation of these supplements on human behavior more specifically.

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