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Recent Updates about the Effects of Vitamin C on the hypothalamic–pituitary–adrenal axis: A review

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ABSTRACT

The HPA axis is a central mediator of the stress response, metabolism balance and immune–neuroendocrine crosstalk. Insight continues to draw attention regarding the control of vitamin C as a crucial cofactor in the regulation at many levels of this axis from neurotransmitter regulation in the hypothalamus to steroid hydroxylation in adrenal gland. This review summarizes current insights in the physiological and molecular interactions by vitamin C with HPA axis, focusing on its involvement in cortisol synthesis, antioxidant system, influencing of ACTH sensitivity and regulating the glucocorticoid-feedback. Special emphasis is placed on advances from experimental, clinical and translational studies which reveal how the availability of vitamin C influences the capacity for stress adaptation, neuroendocrine signalling as well as inflammatory pathways. The review also outlines inconsistencies between studies, methodological considerations and unexamined mechanistic connections that may explain the variation in findings. In summarizing the most recent works, this review presents a comprehensive view of vitamin C–HPA axis crosstalk and its putative clinical relevance in stress-related, metabolic, and inflammatory diseases.

INTRODUCTION

The hypothalamic–pituitary–adrenal (HPA) axis is the prime neuroendocrine system consolidating the mammalian response to physical and psychological stressors, ultimately leading to adrenal glucocorticoid secretion and widespread effects on metabolism, immunity, and behaviour (Patani et al., 2023). HPA axis dysregulation—excessive secretion or blunted secretion of cortisol—has been associated with a number of common disorders, such as major depressive disorder, anxiety, metabolic syndrome and delayed recovery from critical illness. Consequently, both basic investigators and clinicians have high priority interests in identifying safe and inexpensive modulators of HPA-axis activity. One candidate that has garnered renewed interest is vitamin C (ascorbic acid), a small, water-soluble antioxidant and enzymatic cofactor that is highly concentrated in adrenal gland and brain and whose tissue kinetics are altered during stress (Marik, 2020; Travica et al., 2020).

Genetically, vitamin C is at a unique crossroads and can affect HPA-axis function. Beyond its classical functions as an antioxidant, ascorbate is a cofactor for key enzymes in catecholamine and corticosteroid biosynthesis and supports redox-sensitive signalling pathways in adrenal cortical cells (Patani et al., 2023). Studies in animals and in ex vivo systems have reported stress-dependent mobilization of adrenal ascorbate and modulation of steroidogenesis and sympathetic responses by ascorbate availability. These mechanistic associations render plausible the hypothesis that human cortisol responses to acute or chronic stress could be influenced by vitamin C status or supplementation with consequential effects on mood, cognition and cardiometabolic physiology (Marik, 2020; Travica et al., 2020).

The empirical literature surrounding vitamin C and stress physiology has grown and become more varied in scope over the last 10 years. Initial human experimental research indicated that a high-dose of sustained-release ascorbic acid attenuated the blood pressure responses and facilitated the recovery of salivary cortisol to an acute psychosocial stressor (Brody et al., 2002). Since then, more recent randomized as well as quasi-experimental clinical studies in populations with low or suboptimal vitamin C status (Sim et al.,

2022) have found that oral ascorbic acid supplementation (common doses ~500–1000 mg/day) is able to enhance markers of mental vigor, attention performance and subjective stress in these populations. Most conspicuous to date, a randomized trial and subsequent controlled clinical work showed that two months of high-dose 1,000 mg/day ascorbic acid lowers high plasma cortisol and DHEA-S levels in women with functional hypercortisolemia—a finding that would represent the most unambiguous evidence of the ability of vitamin C to mitigate HPA hyperactivity in humans to date, if replicated (Beglaryan et al., 2024).

Two themes have been emphasized in systematic and narrative syntheses since 2018. First, vitamin C has effects that are quantifiable in conditions of physiological or psychological stress or low baseline ascorbate status, but does not at the same above population level when healthy, replete cohorts are considered (Patani et al., 2023; Travica et al., 2020). Second, the degree and direction of endocrine changes seem to be context-dependent (vitamin C can support catecholamine synthesis in some settings and "brake" excessive cortisol responses in others, presumably through antioxidant-mediated modulation of adrenal steroidogenic pathways and central feedback circuits. These complex, occasionally paradoxical results highlight the requirement for vigilant phenotyping (baseline condition, stressor type, sex, and comorbidity) in forthcoming trials (Marik, 2020, Patani et al., 2023).

This emerging evidence places vitamin C as a biophysically plausible, yet clinically attractive HPA axis modulator. However, there are still lacunae: most trials performed to date are small, heterogeneous with their dose and duration, and often surrogate or subjective endpoints are used instead of serial endocrine profiling. Despite several avenues of investigation into the connections between behavior, metabolism, immunity and psychology in humans, there has been limited mechanistic work—connecting tissue ascorbate kinetics, adrenal secretion patterns and HPA regulatory peptides like CRH/ACTH dynamics (Carr & Maggini, 2017).

Thus, an up-to-date, in-depth review that consolidates findings from recent randomized trials, observational cohorts, and mechanistic studies is significant. This review will characterize the human and translational evidence regarding the action of vitamin C on HPA-axis hormones, critically review methodological strengths and limitations of current trials, and recommend areas of investigation that might elucidate whether there are reproducible clinical benefits of vitamin C supplementation for stress-related endocrine dysregulation.

Physiological impact of vitamin C on the HPA Axis

Ascorbic acid (vitamin C) is a central physiological regulator of the hypothalamic–pituitary–adrenal (HPA) axis, a major neuroendocrine system that orchestrates the response to stress. While vitamin C is known to be an antioxidant, it is gaining more attention for its direct contribution to adrenal hormone biosynthesis, redox homeostasis, as well as for its modulation of signaling pathways that can affect the activity of the HPA axis (Patani et al., 2023). Vitamin C displays some of the highest concentrations in the adrenal glands from all human tissues and the levels sharply & dynamically drop during acute and chronic stress indicating that the ascorbate is closely linked to the neuroendocrine regulation (Marik, 2020).

Facilitation of the HPA axis occurs centrally, initiating in the cortex, where corticotropin-releasing hormone (CRH) is released in the hypothalamus. CRH promotes secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which stimulates the adrenal cortex to produce glucocorticoids (chiefly cortisol). Vitamin C plays a role in many steps of this process. One of the major physiologic functions of it is its role as a cofactor for enzymes that are involved in steroidogenesis and catecholamine synthesis. In the adrenal medulla, ascorbate is a co-factor for dopamine β-hydroxylase, the critical enzyme catalyzing the conversion of dopamine to norepinephrine, and indirectly affects the formation of epinephrine (Patani et al., 2023). The adrenal vitamin C is depleted very quickly during the time of stress when catecholamine release is increased significantly and so its ample supply is important for sustaining adrenal hormone production (Travica et al., 2020).

In the adrenal cortex, vitamin C plays a role in the production of glucocorticoid via both enzymatic and antioxidant mechanisms. Within the adrenal cortex, steroidogenic enzymes function in an oxidative milieu and their activity is sensitive to intracellular redox state. Tetrahydrobiopterin is the necessary cofactor to perform the early steps in steroid biosynthesis and ascorbate supports the recycling of this cofactor and other important cofactors for cholesterol transport and steroid hormone synthesis (Marik, 2020). Additionally, oxidative stress from glucocorticoid synthesis may sully adrenal activity when inadequately neutralized by antioxidants. Furthermore, vitamin C also reduces oxidative stress through quenched ROS and maintains the integrity of steroidogenic pathways to provide sufficient Cortisol synthesis (Sim et al., 2022).

In addition to its direct effects on production of adrenal hormones, vitamin C regulates feedback control within the HPA axis. Normally, the high cortisol inhibits the hypothalamus and pituitary with negative feedback. This circuit is disrupted by chronic stress and oxidative assault. Vitamin C has antioxidant function, helping to maintain neuronal and glial cell redox balance, which protects CRH-producing neurons in the hypothalamus from becoming unresponsive to cortisol. This implies that sufficient vitamin C state may prevent the maladaptive rises in cortisol that mark chronic stress and hypo- or hyperactivity of HPA axis (Patani et al., 2023).

A second crucial physiological connection relates to the modulation of inflammatory processes. This bidirectional interaction between hypothalamic–pituitary–adrenal (HPA) axis activity and inflammatory cytokines is well documented, as chronic inflammation is a well-known potent stimulus of HPA axis activity. Vitamin C decreases systemic inflammation via its ability to scavenge reactive oxygen species (ROS), suppress NF-κB–mediated inflammatory signaling, and promote endothelial preservation.

Ascorbate indirectly mitigates inflammatory activation of the HPA axis through these pathways, which may contribute to more stable cortisol rhythms (Travica et al., 2020).

Recent human investigations point to the availability of vitamin C as a determinant of cortisol response to stress for instance demonstrated that higher vitamin C depletion caused either greater or no peaks of cortisol responses during psychosocial or physical stress, while with supplementation the peak was blunted and the recovery faster. Such functional findings further corroborate mechanistic data that suggest ascorbate plays a role in enabling appropriate HPA axis activation during adaptive stress response states but limiting excessive glucocorticoid exposure during states of chronic stress (Beglaryan et al., 2022).

Altogether, the physiological connections of vitamin C to the HPA axis suggests an elaborate coordination of biochemical, endocrine, and antioxidant processes. Vitamin C underpinning adrenal hormone synthesis, influence of central regulatory pathways, antioxidant and pro-inflammatory homeostatic defence, and efficient feedback inhibition of cortisol release. This functional versatility may explain the quick mobilization and depletion of this micronutrient in the face of stressors, as well as the need for high vitamin C status to maintain neuoendocrine homeostasis (Padayatty et al, 2007). This knowledge of physiologically-based links is essential for interpreting recent clinical studies and will guide future studies investigating vitamin C as a potential modifier of endocrine imbalance caused by stress.

Pathophysiology of CSF disorders

Over the last ten years more studies have repeatedly become available indicating a modulatory impact of vitamin C towards stress hormone dynamics, particularly cortisol secretion by HPA (hypothalamic-pituitary-adrenal) axis function. Recent clinical trials and mechanistic studies published after 2015 provide diverse evidence that vitamin C supplementation reduces the physiological and psychological effects of acute stress even in low (and previously ineffectual) doses and can improve resistance to stress. These results support a role of vitamin C as neuroendocrine modulator rather than an antioxidant vitamin (Prevatto et al, 2017).

Among one of the recent noteworthy additions to this literature is a study by Al-fahham (2019) that tested low-dose vitamin C on stress response during a public speaking task, a validated model for acute psychological stress. Public speaking is a well-characterized activator of the HPA axis that commonly elicits sharp peaks in cortisol and quantifiable physiological arousal. In Al-fahham's (2019) RCT the group receiving a low daily dose of vitamin C also significantly attenuated public speaking-related elevations in cortisol when compared to controls. The vitamin C group demonstrated significantly lower subjective stress scores and received higher scores on composure during the group presentation. This study is unique in regard to its importance, as it suggests that even small doses of vitamin C (in doses likely attainable by the average human) can attenuate acute HPA axis activation across potent stressors found with real-life performance protocols. In contrast to previous studies where pharmacological megadoses were administered, the present study demonstrates that even only very low dosed supplementation is capable of exerting endocrine and psychological effects (Dhotre et al., 2025).

These results are further supported and extended by other recent studies. Sim et al. (2022) conducted a randomized controlled trial with healthy young participants and found that 1,000 mg/day of vitamin C for eight weeks increased subjective vitality and emotional well-being. While a direct measure of cortisol was not taken, the investigators suggested that increased mental vitality reflected enhanced neuroendocrine stability, for which vitamin C has a documented role in adrenal activity [14]. These findings support the work of Al-fahham (2019), indicating that vitamin C's regulation of stress may become more evident in young adults experiencing recurrent academic or performance-based stress.

Additional support for this comes from clinical studies of individuals with elevated baseline HPA activity. Beglaryan et al. (2024) reported that 1,000 mg/day vitamin C supplement significantly decreased plasma cortisol and DHEA-S in women with functional hypercortisolemia. This controlled trial is important because it substantiates biochemically that vitamin C can downregulate the production of stress hormones in chronically stressed artifacts. When juxtaposed with the results of Al-fahham (2019) more acute stress investigation, these data support that vitamin C may have a dualistic regulatory mechanism over short- and long-term on cortisol biosynthesis and secretion.

Clinical observations are also further underpinned by mechanistic understanding. Vitamin C is directly involved in adrenal steroidogenesis through redox-based enzymatic pathways within the adrenal cortex (Patani et al., 2023). With stress, there is a massive accumulation of reactive oxygen species in the adrenal tissue and vitamin C serves as an important antioxidant redox buffer to prevent disruption of cortisol synthesis by oxidation. This intertwine action of the molecule gives an obvious potential explanation for attenuated cortisol peaks in clinical stress experiments. Furthermore, vitamin C seems to preserve the sensitivity of negative HPA axis feedback mechanisms, thus preventing exaggerated or prolonged release of cortisol (Travica et al., 2020).

One key theme of recent studies is the role of the baseline vitamin C status in determining responsiveness to supplementation. In people with low or marginal plasma ascorbate levels (prevalent among students, shift workers and those affected by chronic stress), the decrease in cortisol levels and increase in the capacity to cope with stress are even more marked after supplementation (Sim et al., 2022; Travica et al., 2020). Indeed, the results of Al-fahham (2019) bear this pattern out as participants were subject to academic stress and as such may have had suboptimal vitamin C status. This indicates that vitamin C's stress-modulating effects might occur according to a threshold model in which supplementation is most beneficial among individuals with low ascorbate status.

Taken together, recent studies have suggested that supplementation with vitamin C can exert a moderating effect on cortisol secretion, and mitigate the stress response to acute and chronic stressors. Evidence from controlled psychosocial stress paradigms (including the public speaking model used by Al-fahham, 2019) shows that even small doses of vitamin C can attenuate HPA hyperactivity. Clinical trials in patients with endocrine dysfunction provide additional evidence for a potential role for vitamin C in normalizing stress hormone levels. Taken together, these lines of evidence support vitamin C as a potentially promising, safe and accessible stress modulator justifying further study of optimized dosing and targeted therapies for stress-related endocrine dysregulations.

Clinical Aspects of vitamin C impact on stress

Based on the recent developments in nutrition neuroscience and endocrinology, scientific attention is now being refocused on vitamin C as a modulator of hypothalamic–pituitary–adrenal (HPA) axis behavior and psycho- physiological dynamics. Considering the growing body of evidence relating vitamin C to cortisol homeostasis, oxidative defense of adrenals and emotional responses, potentially relevant clinical applications are suggested in a wide array of conditions characterized by acute or repeated stress. However, there are a number of literature limitations, several gaps of knowledge that clearly need improved study designs, more extensive mechanistic knowledge and interventions aimed at indicating the therapeutic potential for vitamin C (Kokoris et al., 2024).

One of the most clinically significant implications is that vitamin C has potential to reduce cortisol levels following exposure to acute psychological stress. Public speaking stress, academic examination stress and short-term performance-based stressors reliably elicit HPA activity. Research using these same animal models demonstrates that those individuals with adequate vitamin C intake have reduced cortisol spikes and a faster recovery back to baseline following stress. For example, Carrillo et al. (2008) showed that vitamin C consumption lowered the ST-induced salivary cortisol elevation in subjects engaged in highly demanding cognitive tasks. This is in agreement with the results of Al-fahham (2019), whose training showed that vitamin C at a small dose reduced cortisol increased in response to group presentation stress, which could indicate that even mild supplementation can dampen acute stress reactivity in students. These findings indicate the potential value vitamin C may have in enhancing cognitive and affective staff performance under acute stress.

The clinical significance is in addition reflected upon chronic stress and burn out which are characterised by sustained cortisol exposure resulting in fatigue, disturbances of the mood and immune function suppression. Poljsak and Milisav (2018) additionally reported that certain micronutrients with antioxidant activities, i.e., vitamin C, can counteract oxidative and endocrine disturbances due to chronic exposure to stress. Similarly, it was found that disrupted cortisol rhythms in those with poor micronutrient status and hypothesised that correcting antioxidant status might improve HPA feedback regulation. These results suggest possible applications of vitamin C to burnout patients and those who are vulnerable to stress-induce psychological problems such as chronic fatigue or depression (Lopresti, 2020).

Vitamin C is also becoming recognized as an adjunct in somatic problems involving HPA dysregulation, including chronic fatigue syndrome, post-viral syndromes and metabolic disorders. For example, de Oliveira et al. (2019) reported fatigue was lowered and overall well-being increased by the intravenous infusion of vitamin C in a cohort of stressed subjects with low baseline values for ascorbate. Cortisol levels were not assayed, however improvement in symptoms parallels effects of HPA normalization. This raises the question of whether vitamin C might be involved in returning an endocrine imbalance to normal under physiologic or inflammatory stress conditions (Suh et al., 2012).

Although there are encouraging discoveries, the field still encounters numerous knowledge deficits. A major factor is the absence of standardized dosing recommendations. Together, studies also tend to use very different amounts of the drug—from low oral doses as in Al-fahham (2019), and moderate daily supplementation, to very high intravenous doses—so it is difficult to provide evidence-based advice. Comparative dose–response studies will be required to evaluate the minimum effective dosage of both acute and chronic stress modulation.

Another major gap is the baseline status of vitamin C, something that is not usually measured or considered for inclusion in trials. Carr and Lykkesfeldt (2021) found that vitamin C-depleted persorns experienced an enlarged cortisol response gem oxidative stress. However, the majority of clinical trials don't stratify subjects according to plasma ascorbate concentration (PA), and this lack of consistency might mask actual effect sizes. Analyses should include baseline nutritional status biomarkers to see whether vitamin C supplementation is more effective for those who are deficient or marginal (Moabedi & Milajerdi, 2025).

An additional limitation is the paucity of long-term randomised controlled studies on chronic outcomes in the HPA axis, diurnal cortisol rhythms or long-term psychological health. Existing research primarily examines acute stress inductions. Although informative, such experiments do not adequately model chronic conditions (e.g., anxiety disorders, burnout, or metabolic syndrome), where HPA dysregulation is sustained over time. Prospective studies with repeated measures of cortisol, sleep and mental health would shed light on longer-term effects (Adam et al., 2017).

Mechanistic research also remains incomplete. While the antioxidant and enzymatic properties of vitamin C in the adrenal gland are understood, relatively few studies exist to address CRH- or ACTH-mediated modulation, receptor sensitivity, or intracellular

steroidogenic pathways. Exploration of these mechanisms with neuroimaging, endocrine profiling, and metabolomics would enhance insight into the physiological influences exerted by ascorbate (Prevatto et al. 2017). Finally, the interplay of vitamin C with other micronutrients or lifestyle variables deserves more attention. Studies by indicate the quality of dietary patterns, sleep, and co-supplementation with magnesium or B vitamins affect the stress response pathways. It is possible that vitamin C interacts with other vitamins, which deserves further study (Zhang et al., 2024).

CONCLUSION

Vitamin C is involved in the physiological function of the HPA axis though its antioxidant properties, cofactor role in adrenal synthesis and modulation of cortisol regulation. Recent research points also to potential for dampening stress-induced hormonal responses and promoting psychological resilience and evidence is emerging even from low-dose supplementation with public-speaking stress. Despite encouraging results, variation in dose, duration and populations studied limit the applicability of existing evidence. Further large, long-term clinical trials are required to elucidate mechanisms as well as optimal intake levels and population-specific effects. In general, vitamin C appears to be an available and biologically feasible adjunct for the empathetic management of stress-related endocrine dyscrasia.

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