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Stimulation of cortisol secretion by caffeine during waking hours in relation to caffeine intake levels - A review of the evidence

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1. ABSTRACT

The analyzed study evaluated whether daily caffeine consumption reduces the response of cortisol, a hormone involved in the stress response, to subsequent doses of caffeine. In a randomized, double-blind, crossover trial conducted on 96 healthy young adults, caffeine increased salivary cortisol after five days without caffeine. After five days of daily intake, the response to the morning dose was attenuated, while an increase reappeared in the afternoon.The research contributes to the narrative of "The Choice to Live Healthy or Sick" by Dr. A. Colonnese and R. Panzironi, according to which caffeine can activate the hypothalamic-pituitary-adrenal axis, the hormonal system of the stress response. Independent studies confirm the acute increase in ACTH and cortisol, but do not demonstrate that this phenomenon causes insulin resistance or persistent metabolic damage in healthy consumers. A subsequent controlled study did not detect changes in the circadian rhythm of cortisol after ten days of caffeine.

ONLINE ARTICLE

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MISSION

LIFE Science Hub – Journal of Science was founded with the aim of making scientific knowledge accessible without giving up methodological rigour, quality of sources and authoritativeness of content. The journal promotes the dissemination of knowledge in the health, nutrition, medical and longevity sciences, building a bridge between the world of research and society.

Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The research question was whether the body develops tolerance to caffeine's ability to increase cortisol throughout the day. Cortisol is a hormone produced by the adrenal glands that participates in the regulation of the stress response, blood pressure, and energy availability. The hypothesis was that controlled daily caffeine consumption could reduce the hormonal response to subsequent doses, without necessarily eliminating it.This question is relevant to paragraph 4.16 because the publication subject to the Evidence Review documents a specific segment of the narrative: caffeine intake can stimulate the hypothalamic-pituitary-adrenal axis, known as the HPA axis, and increase cortisol even in healthy young adults. The study did not measure insulin sensitivity, post-meal glycemia, GLUT4 transporters, or insulin resistance. Therefore, it cannot demonstrate that the observed increase in cortisol alone produces the broader metabolic consequences described in the book's paragraph.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study was a four-week, randomized, double-blind, crossover trial. Randomized means that the order of the conditions was assigned by chance; double-blind means that neither the participants nor the researchers knew which treatment was being received at any given time; crossover indicates that each participant underwent multiple experimental conditions.96 healthy adults completed the study: 48 men and 48 women. Each week, participants avoided dietary caffeine for five days and instead took capsules totaling 0, 300, or 600 mg of caffeine per day, divided into three doses. On the sixth day, they received capsules containing 0 or 250 mg at 9:00 AM, 1:00 PM, and 6:00 PM. Cortisol was measured in saliva eight times between 7:30 AM and 7:00 PM.

4. RESULTS

In simple terms, after five days without caffeine, the body showed a clear hormonal response to the doses of caffeine consumed throughout the day. Technically, the challenge doses produced a robust increase in overall cortisol on the test day compared to the control, with statistical significance equal to $p < 0.0001$. Such a low p-value indicates that, according to the statistical model adopted, the result would be highly unlikely to have occurred by chance alone.After five days of daily intake of 300 or 600 mg of caffeine, the increase in cortisol caused by the first dose at 9:00 AM was no longer detectable. This suggests partial tolerance to the morning response. However, after the second dose, taken at 1:00 PM, cortisol was once again higher between 1:00 PM and 7:00 PM, with p-values between 0.02 and 0.002. In the evening, levels returned to those of the control.The result directly relevant to the book is therefore that adaptation to daily intake did not completely eliminate cortisol stimulation: the response was attenuated in the morning but still present in the following hours. The abstract does not report separate results by gender; it therefore does not allow us to confirm the claim that the peaks are higher in men.

5. INTERPRETATION

The most immediate biological significance is that caffeine can act as a stimulus for the stress hormone system even when consumed habitually. The body appears to adapt partially to the first exposure of the day, but this adaptation does not equate to a complete disappearance of the response. The documented segment is: repeated caffeine increase in cortisol during part of the day.A possible physiological link is the activation of the HPA axis. The hypothalamus and the pituitary gland are brain structures that regulate the adrenal glands; ACTH, or adrenocorticotropic hormone, is the signal that stimulates these glands to produce cortisol. This interpretation is consistent with experimental studies that have observed increases in ACTH and cortisol following caffeine [1].The decisive limitation is that a transient increase in cortisol does not automatically demonstrate chronic stress, metabolic dysfunction, or insulin resistance. To prove this, studies would be needed that link caffeine exposure, hormonal variations, and metabolic or clinical endpoints over time. The analyzed publication only measured salivary cortisol over the course of a single experimental day.

6. INDEPENDENT SUPPORTING EVIDENCE

A randomized, double-blind, crossover trial conducted on 47 healthy young men provided direct confirmation of the acute activation of the HPA axis. An oral dose of

caffeine of 3.3 mg/kg increased ACTH between 30 and 180 minutes and cortisol between 60 and 120 minutes compared to the placebo. At the peak, approximately 60 minutes after caffeine intake, ACTH was 33% higher and cortisol 30% higher. This study supports the caffeine ACTH cortisol pathway, which biologically explains why caffeine can produce a response similar to that induced by acute stress. The sample included only young men and the observation was of short duration [1].A further independent crossover trial examined 16 healthy men who received, in random order, caffeinated coffee, decaffeinated coffee, or water along with a standardized snack. Caffeinated coffee prevented the normal reduction in serum cortisol concentrations observed in the period following consumption. This result confirms that a beverage containing caffeine, and not just purified caffeine capsules, can keep cortisol higher in the short term. The study was small, limited to men, and did not evaluate the effect of prolonged daily use [2].In two independent samples of young adults, of 128 and 148 participants respectively, habitual caffeine consumption reported by participants was associated with greater cortisol reactivity during a psychosocial stress test in the laboratory. This is observational evidence: it indicates that those who reported higher habitual use showed a more intense cortisol response under specific stress conditions, but it does not prove that caffeine was the sole cause of the difference. The result is, however, consistent with the idea that the HPA axis response can remain relevant in habitual consumers [3].Overall, these publications confirm the main direction observed in the original study: caffeine can increase cortisol and the pituitary signal ACTH in humans. However, none of them demonstrate that the acute or intermittent increase in cortisol directly causes insulin resistance, nor that the response is inevitably harmful in every context.

7. CONFLICTING EVIDENCE

A randomized, double-blind, within-subject design trial studied 20 young men who were habitual caffeine consumers. Participants took 150 mg of caffeine three times a day for ten days, a placebo, or caffeine followed by withdrawal. From the ninth day, salivary cortisol and other parameters were measured for 43 hours under controlled light and posture conditions. The temporal profile of cortisol did not differ significantly between caffeine, placebo, and withdrawal [4].This result does not directly contradict the acute increase in cortisol following single doses, because the study had a chronobiological objective: it primarily verified whether regular intake altered the circadian rhythm of cortisol. However, it indicates that repeated daytime consumption does not necessarily lead to a measurable alteration of the hormone's entire circadian curve. The sample was small and composed exclusively of young men; furthermore, the absence of significant differences does not prove that transient effects cannot exist after single doses.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the review from the independent research used to evaluate the section of the book regarding caffeine, the HPA axis, and cortisol.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Double-blind, crossover RCT	96 healthy young adults, 48 men and 48 women	After abstinence, caffeine increases cortisol; after five days of consumption, the morning response attenuates, but the afternoon response persists	direct confirmation	moderate
[1]	Double-blind, crossover RCT	47 healthy young men	Caffeine increases ACTH by 33% and cortisol by 30% at peak compared to placebo	direct confirmation	moderate
[2]	Crossover RCT	16 healthy men	Caffeinated coffee prevents the post-consumption reduction in serum cortisol observed with controls	direct confirmation	moderate
[3]	Observational with experimental stress	Two samples of young adults, 128 and 148 participants	Reported habitual caffeine use is associated with greater cortisol reactivity to stress	indirect confirmation	low
[4]	Double-blind, within-subject RCT	20 young male habitual consumers	Ten days of caffeine do not significantly alter the circadian profile of cortisol	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed shows that caffeine can increase cortisol throughout the day in healthy young adults. Five days of regular intake reduced the response to the first morning dose, but did not eliminate the increase observed after an afternoon dose. The link between caffeine and acute activation of the HPA axis is well supported by independent evidence in humans.However, caution is necessary when moving from the acute hormonal response to chronic metabolic consequences. The publication did not measure insulin resistance or clinical outcomes; therefore, it does not demonstrate that caffeine-induced cortisol elevation directly causes metabolic dysfunction. This part of the narrative requires validation through longer studies, with direct metabolic measurements and more diverse populations.

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delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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