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The translational aspects of glucocorticoid biorhythmicity in modern therapeutics

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Abstract
Glucocorticoids are a class of steroid hormones, vital for mammalian life. They have a plethora of biological effects, mainly supporting metabolic, cognitive, and immunological functions. The pharmacological use of glucocorticoids makes them one of the most frequently prescribed drugs across all continents, and in all types of forms. Nevertheless, a number of serious adverse effects accompany the prolonged treatment with high doses of glucocorticoids. Research developments over the last 20 years have gradually reshaped the way we think about glucocorticoid-based therapeutics. Aside their circadian rhythm and their delayed regulatory influence over an extensive number of sensitive genes, glucocorticoids also possess an underlying, ultradian rhythm, and also exert rapid, non-genomic effects. The notion that chronicity of glucocorticoid stimulation may differentially modulate the type of biological effects of the hormone brings various chronopharmacological concepts on the table of modern glucocorticoid-based therapeutics.

KEYWORDS
glucocorticoids, biorhythmicity, chronopharmacology, pulsatile hormonal replacement, biosensor-assisted drug delivery systems

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MAIN MESSAGE

Glucocorticoids are a class of steroid hormones, vital for mammalian life. They have a plethora of biological effects, mainly supporting metabolic, cognitive, and immunological functions [1]. The fact that high concentrations of glucocorticoids show a strong immuno-suppressive activity was the key element for their wide use across medical specialties, in conditions where inflammatory responses of non-infectious origin constitute the principal pathophysiological mechanism, such as autoimmune disorders. The pharmacological use of (natural or mainly synthetic) glucocorticoids makes them one of the most frequently prescribed drugs across all continents, and in all types of forms (for example pills for oral use, liquid for intravenous administration or eyedrops, or particles released by pressurized inhalers). Nevertheless, a number of serious adverse effects accompany the prolonged treatment with high doses of glucocorti-

coids: patients may develop iatrogenic Cushing syndrome and/or suffer from various neuropsychiatric symptoms, such as fatigue, mood disorders or memory problems [2]. Given the fact that the levels of glucocorticoids increase in various physiological conditions (for instance, during stress) without causing the aforementioned adverse effects, it is crucial to elucidate the underlying dynamics that determine the biological effects of these hormones, to improve the efficacy and use of them in clinical therapeutics.

Research developments over the last 20 years have gradually reshaped the way we think about glucocorticoid-based therapeutics, although the new pieces of evidence have not been yet translated to a paradigm shift in the clinical setting. Traditionally, two features of glucocorticoid biology were considered as characteristic of these hormones [3]: (a) their circadian rhythm and (b) their regulatory influence over an extensive number of sensitive genes via the glucocorticoid receptor, acting as a transcription factor. Nowadays, these features have been complemented with many other, equally important, adding multiple layers to the complex biology (and pharmacology) of glucocorticoids.

For instance, the biorhythmicity of the natural glucocorticoid secretion by the adrenal glands does not just follow a circadian pattern, but a more complex one, combining circadian with ultradian components [4]. All of these components seem to have a biological significance and, thus, should not be disregarded when applying glucocorticoid-based treatments. Glucocorticoids are secreted periodically, in pulses, multiple times per day by the adrenal glands (ultradian rhythm), but the magnitude of the pulses is (under baseline conditions) determined by the time of the day (circadian rhythm). The ultradian rhythm of the hormonal secretion results from the continuous positive feedforward – negative feedback interplay with built-in delays between the anterior pituitary (stimulating the adrenal glands via corticotrophin (ACTH) to biosynthesize and release glucocorticoids) and adrenal glands (inhibiting the anterior pituitary via glucocorticoids to further release ACTH) [5]. The circadian rhythm superimposes the ultradian, originating from the hypothalamic (corticotrophin releasing hormone-mediated) influence on the anterior pituitary, which changes the sensitivity of the latter to the negative feedback control of glucocorticoids.

Moreover, various sources of evidence indicate that aside the genomic effects produced by the glucocorticoid receptors when activated by the hormone (which are mainly delayed effects), membranous variants of these receptors also trigger rapid, non-genomic processes, thereby significantly increasing the diversity of glucocorticoid functions [6]. When it comes to the brain, this diversity expands even more, since glucocorticoids target a second type of receptors, the mineralocorticoid receptors, with 10-fold greater affinity compared to the glucocorticoid receptors. Different variants of these receptors also produce rapid non-genomic as well as delayed genomic cellular events.

The notion that the chronicity of glucocorticoid stimulation may differentially modulate the type of biological effects of the hormone brings various chronopharmacological concepts on the table of modern glucocorticoid-based therapeutics, especially when it comes to neuropsychotherapeutics and managing brain-related adverse effects. For example, subcutaneous, non-pulsatile glucocorticoid administration correlates with poorer quality of sleep compared to a subcutaneous, pulsatile glucocorticoid delivery, mimicking the physiological complex pattern of the hormonal bioavailability. Similarly, oral treatment as well as subcutaneous non-pulsatile infusion were associated with poorer working memory performance under increased levels of cognitive demands, compared to the optimal, pulsatile treatment. These behavioural findings are coupled with brain imaging findings, showing that the functional connectivity of brain regions underlying emotional processing (amygdala, dorsal striatum, insula, orbitofrontal cortex) affecting attentional bias to and recognition accuracy of emotional cues change depending on the chronicity of glucocorticoid administration. Similarly, resting state networks and mood are also affected by the underlying mode of glucocorticoid biorhythmicity. These findings have been replicated in healthy volunteer studies as well as studies in patients with adrenocortical insufficiency [7-9].

The future of glucocorticoid therapeutics involves the use of biosensor-assisted drug delivery systems, in which dynamic detection of the hormonal biorhythm may determine the amount and temporal pattern of glucocorticoid release.

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CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

REFERENCES

1. Kalafatakis K., Russell G.M., Zarros A., Lightman S.L.: Temporal control of glucocorticoid neurodynamics and its

relevance for brain homeostasis, neuropathology and glucocorticoid-based therapeutics. *Neurosci. Biobehav. Rev*. 61: 12-25 (2016).
DOI: **10.1016/j.neubiorev.2015.11.009**
PMID: **26656793**

2. Schäcke H., Döcke W.D., Asadullah K.: Mechanisms involved in the side effects of glucocorticoids. *Pharmacol. Ther*. 96(1): 23-43 (2002).
DOI: **10.1016/s0163-7258(02)00297-8**
PMID: **12441176**

3. Dickmeis T.: Glucocorticoids and the circadian clock. *J. Endocrinol*. 200(1): 3-22 (2009).
DOI: **10.1677/JOE-08-0415**
PMID: **18971218**

4. Russell G.M., Kalafatakis K., Lightman S.L.: The importance of biological oscillators for hypothalamic-pituitary-adrenal activity and tissue glucocorticoid response: coordinating stress and neurobehavioural adaptation. *J. Neuroendocrinol*. 27(6): 378-388 (2015).
DOI: **10.1111/jne.12247**
PMID: **25494867**

5. Walker J.J., Spiga F., Waite E., Zhao Z., Kershaw Y., Terry J.R., *et al.*: The origin of glucocorticoid hormone oscillations. *PLoS Biol*. 10(6): e1001341 (2012).
DOI: **10.1371/journal.pbio.1001341**
PMID: **22679394**

6. Kalafatakis K., Russell G.M., Lightman S.L.: Mechanisms in Endocrinology: does circadian and ultradian glucocorticoid exposure affect the brain? *Eur. J. Endocrinol*. 180(2): R73-R89 (2019).
DOI: **10.1530/EJE-18-0853**
PMID: **30481157**

7. Kalafatakis K., Russell G.M., Harmer C.J., Munafo M.R., Marchant N., Wilson A., *et al.*: Ultradian rhythmicity of plasma cortisol is necessary for normal emotional and cognitive responses in man. *Proc. Natl Acad. Sci. U. S. A.* 115(17): E4091-E4100 (2018).
DOI: **10.1073/pnas.1714239115**
PMID: **29632168**

8. Kalafatakis K., Russell G.M., Ferguson S.G., Grabski M., Harmer C.J., Munafò M.R., *et al.*: Glucocorticoid ultradian rhythmicity differentially regulates mood and resting state networks in the human brain: a randomised controlled clinical trial. *Psychoneuroendocrinology* 124: 105096 (2021).
DOI: **10.1016/j.psyneuen.2020.105096**
PMID: **33296841**

9. Russell G., Kalafatakis K., Durant C., Marchant N., Thakrar J., Thirard R., *et al.*: Ultradian hydrocortisone replacement alters neuronal processing, emotional ambiguity, affect and fatigue in adrenal insufficiency: the PULSES trial. *J. Intern. Med*. 295(1): 51-67 (2024).
DOI: **10.1111/joim.13721**
PMID: **37857352**