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EDITORIAL

Chrono-targeting the prostate: a hypothesis on circadian regulation of androgen receptor activity in benign prostatic hyperplasia

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Abstract

Despite decades of research, 30–40% of patients with benign prostatic hyperplasia (BPH) remain dissatisfied with conventional therapies, highlighting an unmet need for precision approaches. Emerging evidence from prostate cancer and endocrine systems reveals that androgen receptor (AR) activity follows circadian rhythms—yet this critical dimension is overlooked in BPH management. Here, we propose the chrono-targeting hypothesis: circadian-driven fluctuations in AR signaling modulate lower urinary tract symptoms (LUTS) and influence the efficacy of 5-alpha-reductase inhibitors (5-ARIs). Supporting this, a clinical pilot study (n = 22) identified peak LUTS severity in the afternoon/evening, coinciding with predicted AR activity surges. We further outline three mechanistic pillars: (1) circadian regulation of 5-alpha-reductase activity, (2) rhythmic AR nuclear translocation, and (3) chronotype-dependent treatment responses. By integrating chronobiology into BPH care—such as timed 5-ARI dosing—clinicians could exploit these rhythms to enhance symptom control without additional costs or side effects. This paradigm shift toward circadian-aware urology may bridge the gap between variable drug responses and patient-centered outcomes.

Keywords: Benign prostatic hyperplasia, chronotherapy, circadian rhythms, androgen receptor, lower urinary tract symptoms, 5-alpha-reductase inhibitors, chronobiology, personalized medicine, urology

Introduction

Benign prostatic hyperplasia (BPH) is a highly prevalent and clinically significant condition affecting a substantial proportion of aging men worldwide. Epidemiological studies estimate that up to 70% of men over the age of 60 exhibit histological evidence of BPH, with a considerable proportion experiencing bothersome lower urinary tract symptoms (LUTS) such as urinary frequency, nocturia, and decreased urinary flow. From a pathophysiological perspective, BPH is characterized by progressive proliferation of both epithelial and stromal components of the prostatic transition zone, leading to mechanical obstruction and dynamic alterations in bladder outlet function [1, 2].

The androgen receptor (AR) pathway plays a pivotal role in both the development and progression of BPH. Dihydrotestosterone (DHT), the primary androgen involved in prostatic growth, exerts its effects through AR-mediated signaling, influencing cellular proliferation, apoptosis, and tissue remodeling. Accordingly, current medical therapies, including 5-alpha-reductase inhibitors (5-ARI), which reduce DHT synthesis, and alpha-blockers, which target smooth muscle tone, remain the cornerstone of pharmacological management. However, despite their widespread use, these treatments display variable efficacy across patient populations and are often associated with delayed onset of action or incomplete symptom resolution [3].

One potentially overlooked factor contributing to this variability is the temporal dynamics of AR signaling within prostatic tissue. Recent advances in chronobiology suggest that nuclear receptor pathways, including AR, may exhibit circadian fluctuations in expression, activity, and co-regulator availability. Yet, current clinical practice largely ignores these temporal aspects, focusing solely on drug type and dosage without considering the optimal timing of administration relative to endogenous circadian rhythms. This raises an important and underexplored question: could circadian regulation of AR activity represent a missing dimension in the pathophysiology and

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therapeutic management of BPH?

Background and rationale

Chronobiology—the study of biological rhythms and their regulatory mechanisms—has increasingly clarified the role of circadian timing in diverse physiological and pathological processes. At its core, circadian regulation relies on transcription–translation feedback loops driven by key clock genes such as *BMAL1, CLOCK, PER*, and *CRY*. These orchestrate rhythmic expression of downstream genes involved in metabolism, immune regulation, and hormonal signaling [2-4].

Emerging experimental and clinical evidence indicates that nuclear receptor pathways, including the androgen receptor (AR), are subject to circadian modulation. Specifically, BMAL1 has been shown to regulate AR signaling in prostate cancer cells, affecting both receptor expression and transcriptional activity. While these findings originate primarily from oncological models, it is plausible that similar regulatory dynamics operate in benign prostatic tissue, where androgen-mediated pathways are likewise essential [5-7].

Clinical observations in patients with benign prostatic hyperplasia (BPH) support this notion. Both anecdotal reports and documented cases describe diurnal fluctuations in lower urinary tract symptoms (LUTS), such as urinary frequency, urgency, and nocturia—most pronounced during late afternoon and early evening hours. These patterns suggest intrinsic circadian modulation of prostatic function, potentially driven by time-dependent variations in AR signaling, 5-alpha-reductase activity, and endocrine factors like testosterone and dihydrotestosterone [8-10].

Despite these insights, contemporary BPH management strategies rarely consider circadian biology. Pharmacological treatments—including 5-alpha-reductase inhibitors (5-ARIs) and alpha-blockers—are generally prescribed without regard to dosing time, under the implicit assumption of uniform efficacy throughout the day. This oversight may contribute to the substantial interindividual variability observed in treatment responses [11, 12].

Taken together, these findings support the hypothesis that circadian regulation of androgen receptor activity represents a previously underrecognized factor in BPH pathophysiology and therapeutic response, warranting systematic investigation.

Clinical observations

All participants had undergone standard diagnostic workup, including digital rectal examination, serum prostate-specific antigen (PSA) testing, and transrectal ultrasound, confirming the absence of malignancy or other obstructive causes such as urethral strictures or bladder stones. Median PSA was 2.6 ng/mL (range: 1.1–4.2 ng/mL), consistent with benign pathology and supporting exclusion of occult malignancy. None had a history of prostate cancer or were receiving androgen deprivation therapy.

Inclusion criteria were: age between 58 and 74 years, clinical diagnosis of BPH with persistent LUTS, and PSA levels within the benign reference range. Exclusion criteria included uncontrolled comorbidities likely to influence LUTS (*e.g.*, poorly controlled diabetes mellitus, neurologic disorders, active urinary tract infection), diagnosed sleep disorders, and use of medications known to affect circadian rhythms (such as corticosteroids or melatonin agonists).

To investigate potential circadian influences on benign prostatic hyperplasia (BPH) symptomatology, we conducted a structured observational assessment involving 22 men aged 58–74 years, all referred to a single urology clinic for persistent lower urinary tract symptoms (LUTS). As part of their routine clinical evaluation, patients were asked to complete structured symptom diaries over a two-week period. They recorded the frequency and severity of urinary symptoms across four predefined time blocks:

- Early morning (04:00–08:00)
- Late morning (08:00–12:00)
- Afternoon (12:00–18:00)
- Evening (18:00–24:00)

Symptom severity was self-rated using a standardized Likert scale from 0 (no symptoms) to 5 (very severe symptoms), focusing on urinary urgency, frequency, nocturia, and weak stream.

Analysis of the symptom diaries revealed consistent diurnal patterns across most participants. Peak LUTS severity was predominantly reported during the afternoon and evening periods (12:00–24:00), with the lowest symptom burden observed in the early morning. These patterns were consistent regardless of concomitant medication use and independent of variations in fluid intake or physical activity, as assessed through parallel lifestyle questionnaires.

All patients were assessed and monitored within a single medical center, ensuring uniformity in clinical protocols, diagnostic procedures, and data collection methods.

These clinical observations support the hypothesis that androgen receptor (AR) activity and prostatic responsiveness may be subject to circadian modulation, influencing both the timing and intensity of LUTS in BPH patients. While preliminary, these findings highlight the importance of considering temporal patterns in symptom evaluation and therapeutic decision-making. Further prospective studies, incorporating objective urodynamic assessments and diurnal hormonal profiling, are warranted to validate and expand upon these observations.

Chrono-targeting hypothesis

Building upon clinical observations and emerging molecular evidence, we propose the concept of chrono-targeting the prostate as a novel framework for understanding and managing benign prostatic hyperplasia (BPH). This hypothesis posits that androgen receptor (AR) activity and its downstream signaling pathways in prostatic tissue are subject to circadian regulation. Fluctuations in AR respon-

siveness over the 24-hour cycle may directly shape both lower urinary tract symptom (LUTS) patterns and patient-specific therapeutic outcomes.

We hypothesize three principal mechanisms underlying this phenomenon:

1.Circadian modulation of 5-alpha-reductase activity

5-Alpha-reductase, the enzyme catalyzing the conversion of testosterone into dihydrotestosterone (DHT), is central to prostatic growth and AR activation. Evidence from other endocrine systems suggests that enzymatic activity may follow circadian oscillations, driven by clock gene expression and metabolic regulators. If similar rhythms exist in prostatic cells, the timing of 5-alpha-reductase inhibitor (5-ARI) administration could influence DHT suppression efficacy. Morning versus evening dosing may therefore yield distinct clinical outcomes in terms of symptom control and prostate volume reduction.

2.Rhythmic regulation of AR nuclear translocation and co-regulator dynamics

Beyond ligand binding, AR function depends on its nuclear translocation and interaction with transcriptional co-regulators. Circadian modulation of nuclear receptor trafficking and co-regulator availability has been described in systems such as glucocorticoid receptor signaling. We propose that similar temporal dynamics govern AR behavior in benign prostatic tissue, influencing transcriptional activity in a time-dependent manner.

While specific AR co-regulators and clock-controlled genes involved in benign prostatic tissue remain to be identified, we speculate that co-regulators such as SRC family members and nuclear receptor co-repressors (NCoR) may participate in circadian modulation of AR activity, based on parallels from other endocrine tissues.

This could partly explain observed diurnal LUTS fluctuations and variability in AR-targeted therapy responses.

3.Interindividual variability in circadian phase alignment

Circadian phase preferences—or chronotypes—vary among individuals, influenced by genetic, environmental, and lifestyle factors. Such variability may contribute to heterogeneity in BPH symptom patterns and treatment outcomes. For instance, patients with morning-aligned AR activity may experience different symptom trajectories compared to those with evening-aligned profiles. Personalized chronotherapy—aligning treatment timing with each patient's circadian phase—could therefore offer a more precise and effective approach to BPH management.

The chrono-targeting hypothesis suggests that both BPH pathophysiology and therapeutic response are influenced by circadian mechanisms. This underscores the clinical potential of time-adapted therapies that consider not only what is administered but also when, offering a more nuanced and patient-centered strategy for managing BPH.

Conclusions

Circadian regulation of androgen receptor (AR) signaling may represent an underexplored factor in the pathophysiology of benign prostatic hyperplasia (BPH). The chrono-targeting hypothesis posits that fluctuations in AR activity, 5-alpha-reductase function, and hormonal rhythms could modulate lower urinary tract symptom (LUTS) patterns and contribute to interindividual variability in disease expression.

We advocate for future studies aimed at elucidating circadian expression profiles in prostatic tissue and investigating whether aligning treatment timing with intrinsic biological rhythms could offer new avenues for optimizing BPH management. Establishing such temporal dimensions may refine current urological practice, moving toward more biologically coherent, patient-centered strategies.

Declarations

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