International Conference on Women Health

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Evaluation of Circadian Rhythm Disruption in the DHT-Induced Rat Model of PCOS, Exploratory Pharmacological Modulation with Niclosamide

Abstract:

Polycystic ovary syndrome (PCOS) is associated with endocrine and metabolic dysfunction, with increasing evidence implicating circadian rhythm disruption as both a contributing factor and a hurdle to translatability in certain models due to minimal endogenous estrogen present in the DHT-induced model of PCOS. Integrating circadian endpoints is critical, as misaligned rhythms can exacerbate metabolic and reproductive abnormalities, influencing both disease progression and therapeutic effects. Despite this, circadian measures are not routinely incorporated into preclinical PCOS models, limiting evaluation of temporal disease biology and pharmacological response.

This study employs a dihydrotestosterone (DHT)-induced rat model of PCOS to assess circadian disruption and its modulation by niclosamide. Female rats were assigned to three groups (n=6/group): control, DHT, and DHT + niclosamide. A PCOS-like phenotype was established via continuous DHT exposure during the peripubertal period, followed by therapeutic initiation of niclosamide.

Circadian rhythmicity was assessed using continuous home-cage activity monitoring, enabling longitudinal evaluation of rhythm amplitude, phase distribution, and light–dark activity patterns, as well as wakefulness and sleep time patterns. At termination, ovarian and hepatic tissues were collected at defined Zeitgeber timepoints to quantify expression of core clock genes BMAL1, CLOCK, and PER2.

This signal-finding pilot evaluates whether circadian endpoints provide added resolution beyond conventional reproductive and metabolic readouts. We hypothesize that DHT induces circadian disruption, reflected by altered behavioral rhythmicity and dysregulated clock gene expression, and that niclosamide may partially restore these patterns.

These findings support integration of circadian biology into preclinical PCOS models and position temporal endpoints as value-added tools in early-stage drug development and translational study design.