INDIAN SOCIETY FOR CHRONOBIOLOGY

SAMAY

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INSIDE

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For Jan 2025 issue,
send your entries to:

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OFFICE BEARERS

Editor's Note

Dear Readers,

The editorial team of the biannual newsletter of the Indian Society for Chronobiology (InSC) is excited to bring to you the July 2024 issue of SAMAY.
We hope you have had a great and fruitful year so far and we wish you all the best for the rest of this year. This issue is focused on “Chronobiology and Human Health.” under which we have included various interesting articles for our readers. The spotlight event for this issue is the International Symposium on Avian Endocrinology which was held from 17-22 March 2024 at CCS University, Meerut. We have also included a section on upcoming events for your ready reference.

The credit for successful publication of this newsletter goes to the editorial board for putting together this issue and to all the members and researchers who contributed and helped us fulfill the deadline.

Please drop us a line (at inscdu@gmail.com) with your suggestions on topics you'd like to see us cover or things that you like or do not like about what we are doing. We look forward for your feedback and suggestions.

Warm Regards
Sangeeta Rani
Editor-in-chief, SAMAY
Indian Society for Chronobiology

From President's desk

Dear Colleagues,
I greet you at the end of the academic session 2023-24, which I hope was as good as possible in your prevailing circumstances. I sincerely wish you and your academic team the best of health, joy, happiness and incremental progress during the next academic session beginning in July 2024.

I congratulate the editorial team of SAMAY selecting the theme for the July 2024 issue as the "Chronobiology and Human Health." Various articles contributed by members on the theme in this issue seem to be very interesting and meaningful. I thank all the contributors, who form a very young group of Indian Chronobiologists, and I do hope that they will have a long-lasting interest in academic affairs of the Indian Society for Chronobiology (inSC).

I have some good news to share since the last 'Samay' went out in January 2024. In collaboration with Chaudhary Charan Singh University, Meerut, the InSC organized a very successful International Symposium on Avian Endocrinology from 17-22 March 2024, in which the participants from almost all continents participated. Subsequently, the InSC has planned several activities to happen during the period from July 2024 to March 2025. Apart from capacity building programs in Anantnag, J&K in August and Mizoram University in mid-September, Pan-India workshop on Neuroendocrinology in RTM University, Nagpur in mid-November, and in JNCASR, Bangalore during late February/ March 2025, the InSC is the co-organizer of an international conference on the theme of "Circadian Rhythms in Health and Diseases: From Discovery to Functions" in the Indian Institute of Technology, Hyderabad. You may already have or will have a formal announcement of these activities in due course of time. I am sure we shall make a collective effort to make these events a grand success.

I look forward to hearing from you about activities that you are currently involved in, or you are planning to do in the next six months. The InSC will support you in all possible ways in conducting an activity that comes under its mandate for which you will need to write a formal request to the Secretary, InSC.

Very best wishes to all of you.

Vinod Kumar
President, InSC

Scribbles from budding chronobiologists

AN ATTEMPT TO UNDERSTAND CIRCADIAN RHYTHMS

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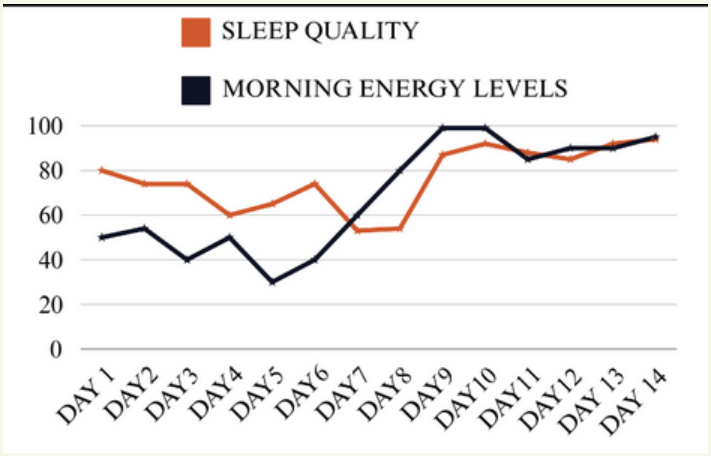
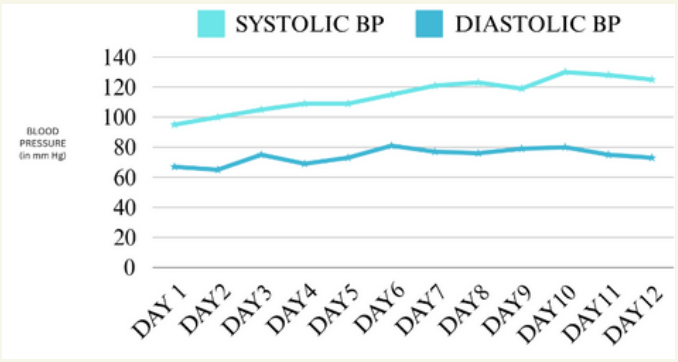
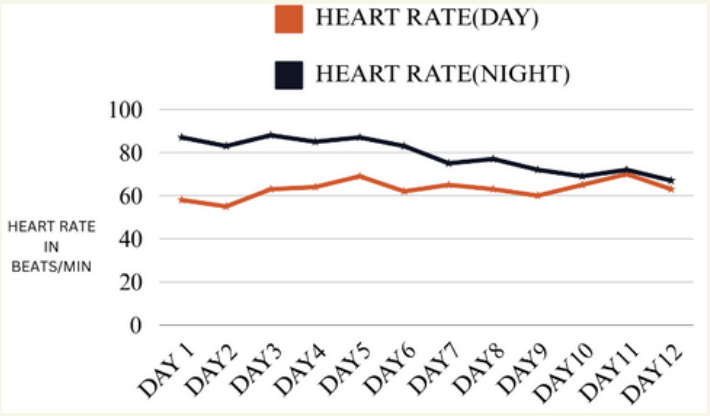
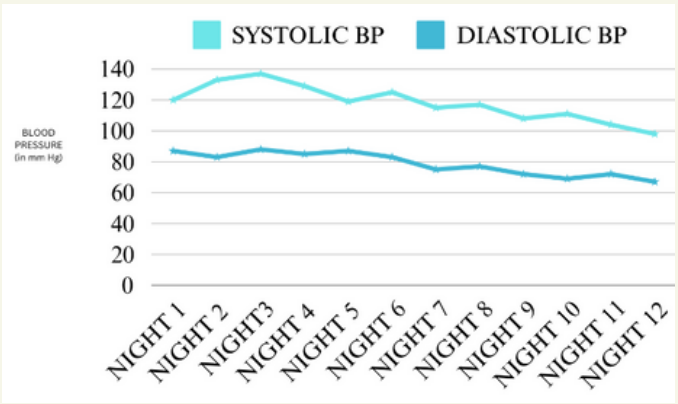
In an attempt to understand circadian rhythms, I conducted a 15-day self-assessment where I adjusted my sleep schedule from my habitual bed time of 1:00AM to 9:00AM to a new regime from 10:00PM to 5:30 AM. I then monitored my blood pressure, SPO2, body temperature, sleep quality and daily energy levels.

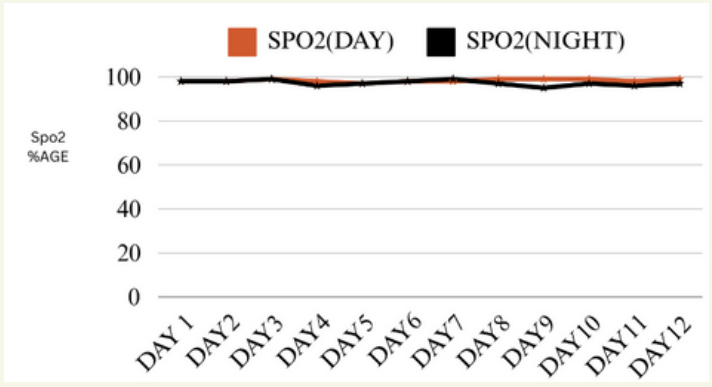
The methodology involved a gradual adjustment to the new sleep schedule, allowing my body to acclimate to the changes.











In my attempt to align my sleep wake cycle with the natural cycle of light and dark, I observed that by the 12th day itself, there was a clear difference in my day and night systolic and diastolic blood pressure, with blood pressure higher during the day and lower towards the night, re-setting the day-night variation. Also, my sleep quality and morning energy levels increased, and the heart rate difference between day and night was reduced.

METABOLIC ALTERATIONS IN HEALTHY HUMAN ADULTS ASSOCIATED WITH CHRONOTYPES- A PILOT CLINICAL TRIAL

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Abstract

Chronobiology pertains to the examination of biological rhythms, specifically the influence of time on biological events and internal biological clocks. Metabolites, which serve as the end products of various metabolic pathways and possess great versatility, are crucial in defining the phenotype of an organism. Therefore, it would be of clinical significance to establish an association between the metabolite signature and chronotype. We conducted an analysis of the chronotypes of eight healthy volunteers using the Munich Chronotype Questionnaire (MCTQ). By employing rapid resolution liquid chromatography - tandem mass spectrometry (RRLC-MS) on serum samples from these volunteers, a comprehensive and unbiased profiling of metabolites was conducted to evaluate the signature metabolites and molecular pathways. Interestingly, the metabolic pathways of Purine, Glycerophospholipid, and Thiamine were noticed to be particularly prominent. When analyzed in the Intermediate and Morning chronotype group, Adenosine triphosphate and glycocholic acid were found to be downregulated, while Phosphoadenosine phosphosulfate was upregulated. Our omics analysis clearly demonstrated a distinct differentiation between chronotypes based on their metabolism and associated pathways; it offers a potential tool for finding marker compounds to assign chronotypes, thereby facilitating the incorporation of chronotherapy in disease diagnosis.

Keywords

Chronotypes, Biomarkers, Human metabolomics, RRLC-ESI-QTOFMS, Circadian rhythm

Introduction

Metabolomics represents the final stage of the -omics cascade and is the nearest to the observable traits (Zhang A et al., 2015). Metabolomics serves as a valuable instrument in the characterization of human physiology, facilitating a more profound comprehension of well-being and illness, assisting in the enhancement of personalized medical approaches, and promoting the advancement of innovative therapeutic strategies (Aderemi et al., 2021).

Individual variation in the functioning of the biological clock is manifested as the chronotype. The chronotype, in biological terms, denotes the individual disparity in

the favored timing of sleep and wakeful activity (Zou H et al., 2022). The distribution of chronotypes within a specific population is influenced by both genetic variations and environmental factors. By considering the variation in the rhythmicity of the clock mechanism, a population can be classified into three primary chronotypes: Morning, Intermediate, and Evening (Roenneberg T et al., 2003). Our proposition involves the evaluation of chronotypes through the identification of metabolite signatures, which serve as biochemical markers for the chronotype.

Ayurveda, an ancient medical science originating in India, places great importance on diet (ahara) and sleep (nidra) as fundamental pillars of health. Ayurvedic body type (Prakriti) is a parallel concept to chronotypes which we are actively pursuing for its correlation. Similarly, Bizzarri and colleagues, 2022 performed a comparable analysis to explore the metabolomic profiles of shift workers. Their findings indicated that male shift workers exhibited higher levels of glycoprotein acetyls (GlycA), triglycerides, and fatty acids compared to non-shift workers. To our current knowledge, no such analysis has been conducted to distinguish chronotypes in humans. Consequently, this study employed a metabolomic approach to construct a PLS-DA based discrimination model to evaluate the chronotypes of individuals and identify the primary metabolic pathways associated with different chronotypes.

Materials and methods

Chronotypes assessment: The chronotype assessment was performed using the Munich Chronotype Questionnaire (MCTQ) (Roenneberg T et al; 2003).

Study design and convenient sampling: Total number of young and healthy volunteers participated in this study was 30 (n=30). It includes 15 females and 15 males in the age group of 20 to 38 years. Only 8 volunteers (n=8, 5 male and 3 females) fulfilled the inclusion criteria out of 30 volunteers. In morning hours overnight fasting 2.5 mL whole blood was collected from participants in BD serum separation tube (BDTM 366882) through the antecubital fossa. Serum metabolites fractions were separated out by solvent precipitation using methanol.

HPLC-Q-TOF-MS analysis: The serum metabolomics samples were resolved on Agilent 1290 Infinity Series UPLC interfaced to an Agilent 6538 Accurate-Mass Q-ToF MS. A volume of 15 µL of each sample was injected into an assembly of C18 ZORBAX (4.6 x 12.5 mm) guard column followed by C18 (4.6 x 150 mm) HPLC column of particle size 5.0 mm. The solvent system had (A) 0.1% formic acid-water and (B) 0.1% formic acid-acetonitrile in gradient mode. The mass spectrometer was operated in positive ion polarity mode.

Multivariate analysis: Mass Hunter Qualitative Analysis (B.04.00, Agilent Technologies) software was used for preliminary investigation of raw MS/MS data. Mass Profiler Professional (MPP) (B.02.00) and Metaboanalyst tools were used for statistical and pathways-based analysis of the data respectively.

Results

According to the assessment conducted using a questionnaire, the morning chronotype was assigned to three females and four males, while the intermediate chronotype was assigned to a solitary male.

Serum metabolome analysis confirms the alteration in the metabolite expression

The extracted base peak chromatograms (BPC) of 2 chronotypes samples showed distinct peaks. Analysis of total ion

chromatograms showed an average of 25 peaks containing around 1000 compounds In MPP, variability in the peaks was normalized successfully using internal standards and Z-transforms. Reproducible and stable molecular features were subsequently used for statistical analysis.

The well-established PLS-DA regression value 0.94 shows the accuracy of results. The result of the sample classification presented in terms of discrimination ability was found to be 93.75% accurate, representing the percentage of the samples correctly classified during model training and cross-validation (Table 1 available on request). Data were further subjected to T-test unpaired with permutative and Benjamini Hochberg multiple testing correction to validate the PLS-DA model and to further decrease false discovery rate (Table 2 available on request). Both the groups showed considerable variability in metabolomic level and were clearly separated from each other (Fig. 1). Based on Fold changes (>= 2.0) 11 metabolites were found to be significant. Out of these, 9 were downregulated and 2 were upregulated in Intermediate class in comparison to morning chronotype (Table 3 available on request). Phosphoadenosine phosphosulfate and DG (5 -iso PGF2VI/0:0/a-13:0) were the highest abundant upregulated metabolites in Intermediate type.

Qualitative analysis leads to identification of variable metabolites

The list of 35 metabolites obtained through the PLS-DA model has been arranged in descending order of their Variable importance in projection (VIP) score (Suppl. Table 2 available on request). Finally, differentially expressed metabolites in all groups were obtained and identified using standard Metlin library and HMDB.

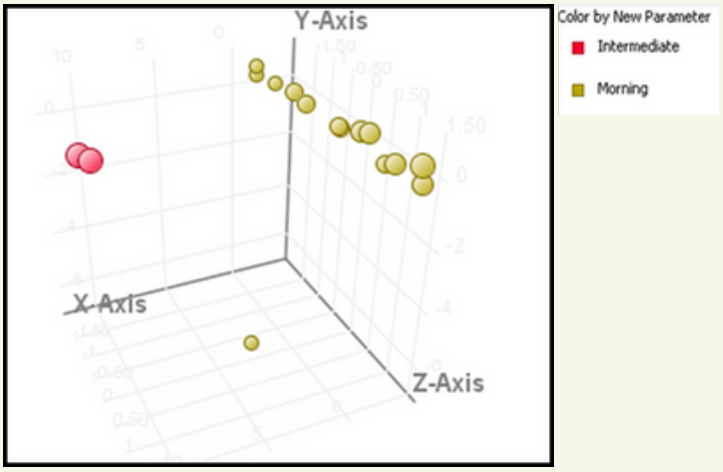

Fig. 1. 3D PCA plot obtained through Partial Least Squares Discrimination analysis (PLS-DA) class prediction model.

Pathway analysis confirms the correlation between chronotypes and associated pathways

Metaboanalyst was employed to investigate the metabolite pathways that were significantly impacted in various chronotypes. The analysis of these pathways revealed that Purine metabolism, Glycerophospholipid metabolism, and Thiamine metabolism were the only pathways that exhibited a statistically significant p value ($p<0.05$). These pathways are associated with the metabolism of nucleotides, vitamins, and lipids, respectively. On the other hand, Sulfur metabolism, Glycosylphosphatidylinositol (GPI)-anchor biosynthesis, Pyrimidine metabolism, Tyrosine metabolism, and Primary bile acid biosynthesis were also suggested as potential pathways by Metaboanalyst, but their p values were greater than 0.05 (Suppl. Table 1 available on request).

Discussion

Link between metabolites expression and circadian rhythm

The metabolome exhibits notable fluctuations throughout the day, particularly in relation to amino acids and multiple lipid classes. A study has been conducted on the impact of circadian and external cycles on the time-of-day

variation in the human metabolome (Hancox TP et al., 2021).

Upregulation of glycerophospholipid, thiamine, and purine metabolism in different chronotypes

We have observed an upregulation of glycerophospholipid metabolism in individuals with an intermediate chronotype, while thiamine metabolism and purine metabolism were upregulated in individuals with a morning chronotype (Supp. Table 1 available on request).

Differential metabolites expression connected with circadian rhythms of different chronotypes

By analyzing circadian blood metabolomics, it is feasible to detect the individual internal body time under different conditions. Utilizing biomarkers in the form of metabolites provides additional benefits, including a close connection to the phenotype of an organism, cost-effective processing, and a shorter turnaround time. The regulation of multiple aspects of human physiology is governed by daily rhythms.

Based on our analysis, we have discovered 11 metabolites that possess statistical significance ($p<0.05$, Fold change $FC>2.0$) and demonstrate the potential to serve as candidate biomarkers. Amongst the Intermediate type, Cyclic GMP and Epinephrine were identified as the most abundant down regulated metabolites. Conversely, Thiamine triphosphate, Glycocholic acid, and Adenosine triphosphate manifested an upregulation in the morning chronotype.

Unfortunately, we were unable to find adequate literary evidence for the remaining group of metabolites in our investigation, namely LysoPC(16:0/0:0), PE(P-16:0/PGJ2), PA(18:3(9,11,15)-OH(13)/i-16:0), Deoxyuridine, and Phosphoadenosinephosphosulfate, that are involved in the regulation of circadian rhythms.

Metabolomics investigations, as opposed to established methods, require only a single instance of sampling (Bizzarri D et al., 2022). In order to curtail the occurrence of false predictions, metabolomics analysis mandates strict inclusion-exclusion criteria, which explains the restriction on the sample size in our current study. Though not many details are available for distribution of chronotypes in young Indian population two reports indicated a trend where the Intermediate chronotype was predominant followed by Morning and Evening type (Sharma A, Kaushik NK 2023). Because of the limitations in our sample size and the absence of all chronotypes, we were unable to establish any connection between pathways or metabolites and the evening chronotype. It is possible that certain metabolites may have been overlooked in our analysis workflow. There is a likelihood that specific pathways, which could be relevant to the evening chronotype, may be absent from our data. The pathways recognized in our data by Metaboanalyst include sulfur metabolism, glycosylphosphatidylinositol (GPI)-anchor biosynthesis, pyrimidine metabolism, tyrosine metabolism, and primary bile acid biosynthesis; however, these pathways were not statistically significant. Nevertheless, some of these pathways are likely to be associated with the evening chronotype. Utilizing metabolomics biomarkers could potentially offer an alternative and accurate means of assessing chronotype. The identification of such biomarkers would greatly contribute to the advancement of sleep and circadian science and chronomedicine.

Conclusion

The present investigation utilized a metabolomic approach to build a Partial

Least Squares Discriminant Analysis (PLS-DA) model to assess the chronotypes of individuals and determine the predominant metabolic pathways linked to various dominant chronotypes. Our findings indicate that Purine metabolism, Glycerophospholipid metabolism, and Thiamine metabolism are key pathways that are significantly linked to morning and intermediate chronotypes, involving a total of 10 differentially expressed metabolites. To enhance the reliability of our findings, it would be advantageous to conduct further analysis using targeted metabolomics, a larger sample size, and advanced bioinformatics tools. Such measures are imperative in order to propose a repertoire of biomarkers for each chronotype with increased confidence.

Ethical clearance

The present clinical trial was approved by the Institutional Ethics Committee of the RAIFR (CCRAS-Ministry of AYUSH), Pune, India wide letter no. 3-47/2017-18/RAIFR/Pune/IEC/1490 dated 02.03.2020. All volunteers signed a written informed consent to be a part of this study. The recruitment period for this study was spanned from 1st December to 6th December 2021.

Acknowledgement

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References

- Aderemi, A. V., Ayeleso, A. O., Oyedapo, O. O., Mukwevho, E. 2021. Metabolomics: A scoping review of its role as a tool for disease biomarker discovery in selected non-communicable diseases. Metabolites. 11(7), 418. doi.org/10.3390/metabo11070418.
- Bizzarri, D., Dollé, M. E., Loef, B., van den Akker, E. B., van Kerkhof, L. W. 2022. GlycA, a biomarker of low-grade inflammation, is increased in male night shift workers. Metabolites. 12(12), 1172. doi.org/10.3390/metabo12121172.
- Hancox, T. P., Skene, D. J., Dallmann, R., Dunn, W. B.2021. Tick-tock consider the clock: the influence of circadian and external cycles on time of day variation in the human metabolome-a review. Metabolites. 11(5), 328. doi.org/10.3390/metabo11050328
- Roenneberg, T., Wirz-Justice, A., Merrow, M. 2003. Life between clocks: daily temporal patterns of human chronotypes. Journal of biological rhythms. 18(1), 80-90. doi.org/10.1177/0748730402239679
- Sharma, A., Kaushik, N. K. 2023. Morningness-eveningness Preferences among Medical Students: A Cross-sectional Study. Journal of Clinical and Diagnostic Research. 17(1), CC01-CC01. doi.org/10.7860/JCDR/2023/57592.17208
- Zhang, A., Sun, H., Yan, G., Wang, P., Wang, X. 2015. Metabolomics for biomarker discovery: moving to the clinic. Biomed research international. 2015. doi.org/10.1155/2015/354671
- Zou, H., Zhou, H., Yan, R., Yao, Z., Lu, Q. 2022. Chronotype, circadian rhythm, and psychiatric disorders: Recent evidence and potential mechanisms. Frontiers in Neuroscience. 16, 811771. doi.org/10.3389/fnins.2022.811771.

CHRONOBIOLOGY OF DISEASES IN HUMANS

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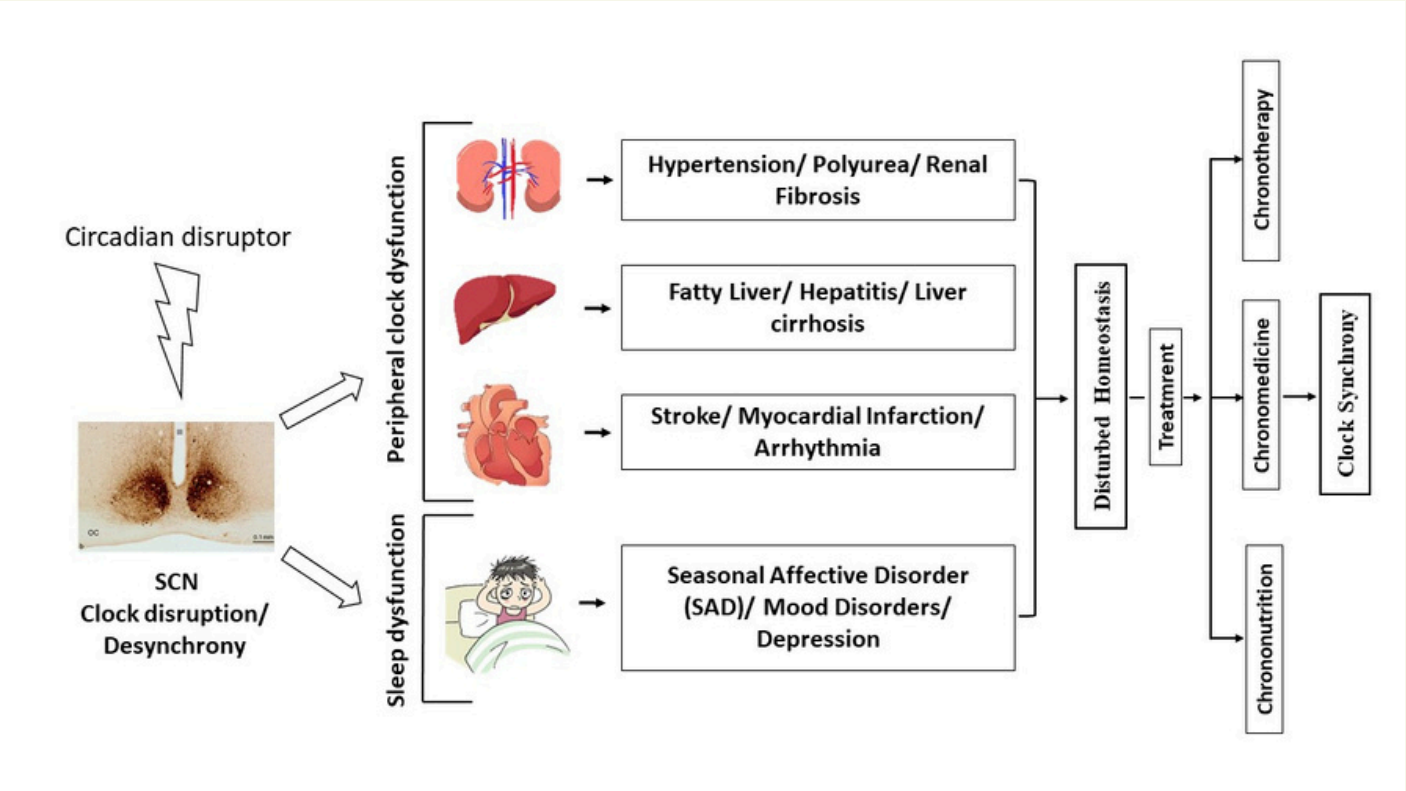
Chronobiology is the study of biological rhythms which depend on the environmental cyclic phenomenon like day/ night or winter/ summer cycle (SRBR). Many diseases or their symptoms show the cyclicity and have been found to be linked to the circadian rhythms. For example, rheumatoid arthritis pain and stiffness mainly occurs in the morning hours because of inflammatory cytokines increase over the night. On the other hand, asthma and allergic rhinitis symptoms peak during the night hours, due to sleeplessness and changed nasal and lung mucosa quality due to circadian rhythms (Craig et al., 2004). Various mood disorders like depression, bipolar disorder, and seasonal affective disorder (SAD) have been found to be linked to disruption in the biological rhythms. Desynchrony between the circadian rhythm and sleep wake cycle due to prolonged shift work and jet lag like condition, can be resynchronized by the external bright light exposure especially blue and green light at appropriate time (Lack & Wright, 2007).

Circadian rhythms are regulated by biological clocks. In addition to the master circadian clock (SCN: Supra chiasmatic nucleus) in the brain, there are peripheral clocks present in different vital organs. Each such peripheral clock maintains the synchrony with the master clock and maintains the homeostasis of the body. For instance, any disturbance in the kidney circadian rhythm could be the reason for hypertension, polyuria and related diseases that might come up with the renal fibrosis (Johnston & Pollock, 2018). Liver functioning on the other hand is also under the control of biological clock. Any clock dysfunction in liver triggers diseases such as liver cirrhosis, hepatitis, fatty liver, and liver cancer. Chrononutrition practices including regulation of food intake and food composition are an emerging area of research to recover from many physiological dysfunctions associated with metabolism (Tahara & Shibata, 2016). Similarly, cardiac system of our body follows a rhythmic pattern. There are several cardiovascular processes such as blood pressure, heart rate, and platelet aggregation that get activated and increased during morning hours. Number of adverse cardiovascular events (stroke, myocardial infarction, ventricular arrhythmias, and sudden cardiac arrest) show an apparent increase during morning hours (06.00–12.00 h). Studies have shown that morning time heart attack have a larger infarct size and worse prognosis, compared to the occurrence of myocardial infarction during the rest of the day (Buurma et al., 2019).

In conclusion, chronobiology has enriched our knowledge to understand the diseases and their management. It is quite evident that our biological clocks, which regulate our homeostasis and physiological processes in a rhythmic manner, play very crucial role in determining the onset, progression, and treatment of various diseases. Incorporating the principles of chronobiology into medical practice could potentially enhance disease prevention strategies, improve diagnostic accuracy, and optimize therapeutic interventions. Such incorporation leads to

development of new management techniques such as chronotherapy and chrononutrition. The study of the chronobiology of diseases is, thus, a promising and exciting frontier in medical research.



References

- Buurma, M., Van Diemen, J. J., Thijs, A., Numans, M. E., & Bonten, T. N. (2019). Circadian rhythm of cardiovascular disease: the potential of chronotherapy with aspirin. Frontiers in Cardiovascular Medicine, 6, 84.
- Craig, T. J., McCann, J. L., Gurevich, F., & Davies, M. J. (2004). The correlation between allergic rhinitis and sleep disturbance. The Journal of allergy and clinical immunology, 114(5 Suppl), S139–S145. https://doi.org/10.1016/j.jaci.2004.08.044.
- Johnston, J. G., & Pollock, D. M. (2018). Circadian regulation of renal function. Free radical biology & medicine, 119, 93–107. https://doi.org/10.1016/j.freeradbiomed.2018.01.018.
- Lack, L. C., & Wright, H. R. (2007). Chronobiology of sleep in humans. Cellular and molecular life sciences, 64, 1205-1215.
- SRBR: Society for Research on Biological Rhythms. What Are Biological Rhythms?
- Tahara, Y., & Shibata, S. (2016). Circadian rhythms of liver physiology and disease: experimental and clinical evidence. Nature Reviews Gastroenterology & Hepatology, 13(4), 217-226. Doi: https://doi.org/10.1038/nrgastro.2016.8.

MALE CHILD AT GREATER RISK: IMPACT OF PROLONGED SCREEN EXPOSURE IN PERINATAL MOTHERS AND THEIR OFFSPRINGS

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With technological advancements and changing lifestyles, screen time usage has occupied a decent slot in our daily lives. Most of us spend at least 1-2 hours gazing at one or the other screen. Although, many of us are aware that prolonged screen time (particularly the blue wavelength emitted by the screens) can affect our well-being in several ways by affecting our circadian rhythms, nevertheless, we cannot completely prohibit its application in our day-to-day lives. However, most of us are unaware of the fact that its consequences could be passed on to the next generation! This short report will shed light upon the recent findings that have shown the effects of prolonged screen exposure in perinatal mothers and their offspring.

COVID19 pandemic posed psychosocial stress on pregnant women. To investigate the patterns of behavioral coping strategies associated with overcoming psychosocial distress during the COVID19 pandemic, a large multicentre sample of pregnant women (N= 2876) and postpartum women (N= 1536) in the United States were studied (Werchan et al. 2022). Four behavioral phenotypes were identified of which passive and active coping behavioral strategies were prominent. Of this, the passive strategy included increased screen time, social media usage, and intake of comfort foods, which was associated with elevated symptoms of depression, anxiety, and global psychological distress, as well as worsening stress and energy levels, while the active strategy included social support and self-care.

This study opened new avenues for early identification of perinatal women at risk for poor long-term outcomes, in case, they opt for passive strategies to cope with stress during pregnancy. In another study based on the same scenario of COVID19 pandemic (Zhang et al., 2021), one large-scale, multicentric cross-sectional study was conducted across middle and Western China, recruiting 1794 pregnant women. The association of sleep duration and screen time with anxiety among these women was addressed. Results proved that longer sleep duration was linked to lower anxiety levels whereas screen time was associated with higher anxiety in pregnant women.

Later on, in 2020, a study (Chen et al., 2020) on 6236 mother-child pairs in Shanghai revealed that prolonged screen exposure, short sleep duration, and lack of physical activity during pregnancy could increase the risk of respiratory allergies during childhood (14.6, 16.2, and 21.0% of children had asthma, wheeze, and allergic rhinitis respectively), particularly in the male child in a dose-response pattern. This was a novel of its kind that showed the direct effects of screen time usage on poor development of the immune system in offspring. Another study in the same year (Sõritsa et al., 2020) evaluated the association of physical activity and sedentary behavior before and during in vitro fertilization (IVF) with controlled ovarian stimulation (COS) and pregnancy outcomes. For this longitudinal study, 107 infertile women undergoing IVF treatment were recruited. . Data on total screen time was assessed using questionnaires. The study showed that women with high total

screen time during non-work days (≥ 7 h) obtained 4.7 oocytes ($p = 0.005$) and 2.8 embryos ($p = 0.008$) less as assessed in CO, thereb indicating that prolonged screen time negatively affects COS outcomes under assisted reproduction methodology.

As sedentary screen time is considered an early, changeable risk factor for obesity and poor child development, to test the relationship between maternal and infant screen time with child growth and development, a longitudinal study assessing screen time (Kracht et al., 2023) was conducted on pregnant mothers, and subsequently in children at 3 months, 12 months, and 24 months of age. It was found that both sexes increased screen time between 12 months and 24 months (*ps* <0.05) of age. Screen time in children was positively associated with adiposity and negatively associated with development scores. Whereas, in adjusted models, screen time was positively associated with adiposity in boys, and meeting the screen time guideline was associated with lower adiposity in girls.

This study suggested that a cautionary approach to screen time early in life may benefit child health. More recently, another research investigation (Kushima et al., 2022) where the association between screen time exposure and Autism Spectrum Disorder (ASD) in Japanese children was carried out in a cohort study, for which the data from 84,030 mother-child dyads were analyzed, it was shown that prolonged screen time at 1 year of age was significantly associated with ASD diagnosis at 3 years of age, and boys were 3 times more likely to have been diagnosed with ASD than girls.

Taking together, these studies highlighted that promoting physical activity and proper sleep duration could improve the mental health of pregnant women in public health emergencies such as COVID19, under psychosocial distress active coping behavior strategy should be acquired, mother's screen time usage can affect a child's immune system, metabolism and mental health, and male children are more prone to such consequences.

References

- Chen Y, Lyu J, Xia Y, Zhu J, Tong S, Ying Y, Qu J, Li S. (2020). Effect of maternal sleep, physical activity and screen time during pregnancy on the risk of childhood respiratory allergies: a sex-specific study. Respir Res. 21(1):230. https://doi.org/10.1186/s12931-020-01497-8.
- Kracht CL, Redman LM, Bellando J, Krukowski RA, Andres A. (2023). Association between maternal and infant screen time with child growth and development: a longitudinal study. Pediatr Obes. 18(7):e13033. https://doi.org/10.1111/ijpo.13033.
- Kushima M, Kojima R, Shinohara R, et al. (2022). Association between screen time exposure in children at 1 year of age and autism spectrum disorder at 3 Years of Age: The Japan Environment and Children's Study. JAMA Pediatr. 2022;176(4):384–391.
- Sõritsa D, Mäestu E, Nuut M, et al. (2020). Maternal physical activity and sedentary behaviour before and during in vitro fertilization treatment: a longitudinal study exploring the associations with controlled ovarian stimulation and pregnancy outcomes. J Assist Reprod Genet. 37(8):1869-1881. https://doi.org/10.1007/s10815-020-01864-w.
- Werchan DM, Hendrix CL, Ablow JC, et al. (2022). Behavioral coping phenotypes and associated psychosocial outcomes of pregnant and postpartum women during the COVID-19 pandemic. Sci Rep. 12:1209. https://doi.org/10.1038/s41598-022-05299-4.
- Zhang Y, Zhang Y, Deng R, et al. (2021). Association of sleep duration and screen time with anxiety of pregnant women during the COVID-19 Pandemic. Front Psychol. 12:646368.

A CASE FOR LARGE SCALE, LONG TERM PROSPECTIVE STUDY OF CIRCADIAN DISRUPTION ON HEALTH AND DISEASE IN INDIAN POPULATION

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As India makes strides towards a developed economy and rapid urbanization, we are already observing the shift towards higher burden of non-communicable lifestyle related diseases. There are several well established factors that contribute to this correlation including sedentary lifestyle, more consumption of high calorie and processed food, exposure to various forms of pollution and stress. Another very important but often ignored factor amongst these is the constant disruption in circadian rhythms owing to artificial light at night, disrupted meal times, overall lack of physical activity and the 24X7 culture. There has been a consistent rise in the artificial light at night in India particularly in the regions that have undergone rapid urbanization (Kumar et al., 2019). The artificial light not only has adverse effects on the circadian rhythms of humans but also on the other flora and fauna. The adverse effect of the artificial light at night on human health and disease is well established (Svechkina et al., 2020). Similarly, there is a change that is visible in the dietary habits in terms of consumption of high calorie, processed and high fat food. Considering close relationship between the time of day specific meals and metabolism, it becomes pertinent to study this with respect to circadian disruption. There is also considerable diversity in the dietary habits across different regions in India and a thorough understanding of how different dietary habits interact with the circadian rhythms and disruption thereof, could provide meaningful insights into the health and disease across India. Finally, single time zone across the easternmost and the westernmost regions of India is a constant circadian disruptor, particularly in the northeastern states with implications on the amount of direct sunlight accessible to the population. A thorough understanding of long-term effects of this on health and disease state of the people living these areas may pave way for policy changes.

Some of the recent efforts in the form of long prospective studies around the world have yielded crucial information about the role of circadian rhythms and lifestyle patterns defining the risk factors related to complex diseases such as type 2 diabetes, Alzheimer's, and cardiovascular pathologies Bai et al., 2024 a, b; Winer et al., 2024. The utilization of longitudinal UK Biobank dataset has been an indispensable resource to understand the cross-talk between circadian rhythms and health outcomes through multiple avenues, ranging from non-invasive methods such as wearable devices to blood based biomarkers, MRIs, and NGS techniques like exome sequencing. A recent study from data on the diurnal rhythms of wrist temperature and its correlation to chronic diseases is set to open up avenues for finding molecular mechanisms behind these correlations (Brooks et al., 2023). This will lead to not only better understanding of complex diseases but perhaps also novel pathways and drug targets. A similar large-scale recent study links shift work

and extreme late chronotypes to non-alcoholic fatty liver disease (Maidstone et al., 2024). Here again, the molecular mechanisms may not be fully understood and a thorough investigation may provide clues to mitigate the dangers associated.

Several large-scale studies towards mapping the genomics and its relationship with diseases in Indian population have been carried out and continue to provide crucial understanding of the health and disease landscape of India. Completion of the 10000 Genome Project in February 2024 is a great milestone example of large-scale studies on Indian population (DBT India). A similar effort in the form Phenome India within Council for Scientific and Industrial Research funded organizations plans to collect crucial phenotypic data in long term observational cohort for health outcomes.

With the advent of AI technologies in the biopharma market, and global projects such as pangenome reference and telomere-to-telomere consortium, the predictions and scope of integrating this information becomes highly likely. Such integrative studies could contribute to understanding the Indian population better with the potential to understand pharmacogenomic outcomes and personalized management opportunities to reduce the health-burden in Indian population with a circadian perspective.

Perhaps it is now right time to undertake a large-scale study of circadian disruption due to multiple factors and their long-term health outcomes in the Indian population. This would require efforts from not only multiple researchers but also multiple agencies and stakeholders. Hence, this forum makes it ideal to start this conversation and come together towards this. The outcomes of such a study certainly will have major implications on the life of millions of Indians.

References

- Bai P., X. Shao, L. Chen, S. Zhou, Y. Lin, H. Liu, P. Yu (2024a); Association between circadian physical activity trajectories and incident type 2 diabetes in the UK Biobank. Sci Rep 14, 6459.
- Bai P., S. Zhou, X. Shao, Y. Lin, H. Liu, P. Yu (2024b); Ideal 24-h physical activity trajectory reduces all-cause, cause-specific mortality and cardiovascular outcomes through aging deceleration and inflammation regulation: A UK biobank study; International Journal of Cardiology, 399, 131770.
- Brooks T. G., N. F. Lahens, G. R. Grant, Y. I. Sheline, G. A. FitzGerald, C. Skarke (2023); Diurnal rhythms of wrist temperature are associated with future disease risk in the UK Biobank; Nature Communications, 14:5172
- https://dbtindia.gov.in/sites/default/files/GenomeIndia-Digest-27-02-2024_1.pdf
- Kumar P., S. Rehman, H. Sajjad, B. R. Tripathy, M. Ranic, S. Singh (2019); Analyzing trend in artificial light pollution pattern in India using NTL sensor's data; Urban Climate, 27, 272–283.
- Maidstone R., M K Rutter, T Marjot, D. W. Ray, M. Baxter (2024); Shift work and evening chronotype are associated with hepatic fat fraction and non-alcoholic fatty liver disease in 282,303 UK biobank participants; Endocrine Connections, 13, e230472.
- Svechkina A., B. A. Portnov, T, Trop (2020); The impact of artificial light at night on human and ecosystem health: a systematic literature review; Landscape Ecol, 35:1725–1742
- Winer J. R., R. Lok, L. Weed, Z. He, K. L. Poston, E. C. Mormino, J. M. Zeitzer (2024); Impaired 24-h activity patterns are associated with an increased risk of Alzheimer's disease, Parkinson's disease, and cognitive decline; Alzheimer's Research & Therapy, 16, 35.

FEAR OF CONNECTION: UNDERSTANDING NOMOPHOBIA AND ITS HEALTH RAMIFICATIONS

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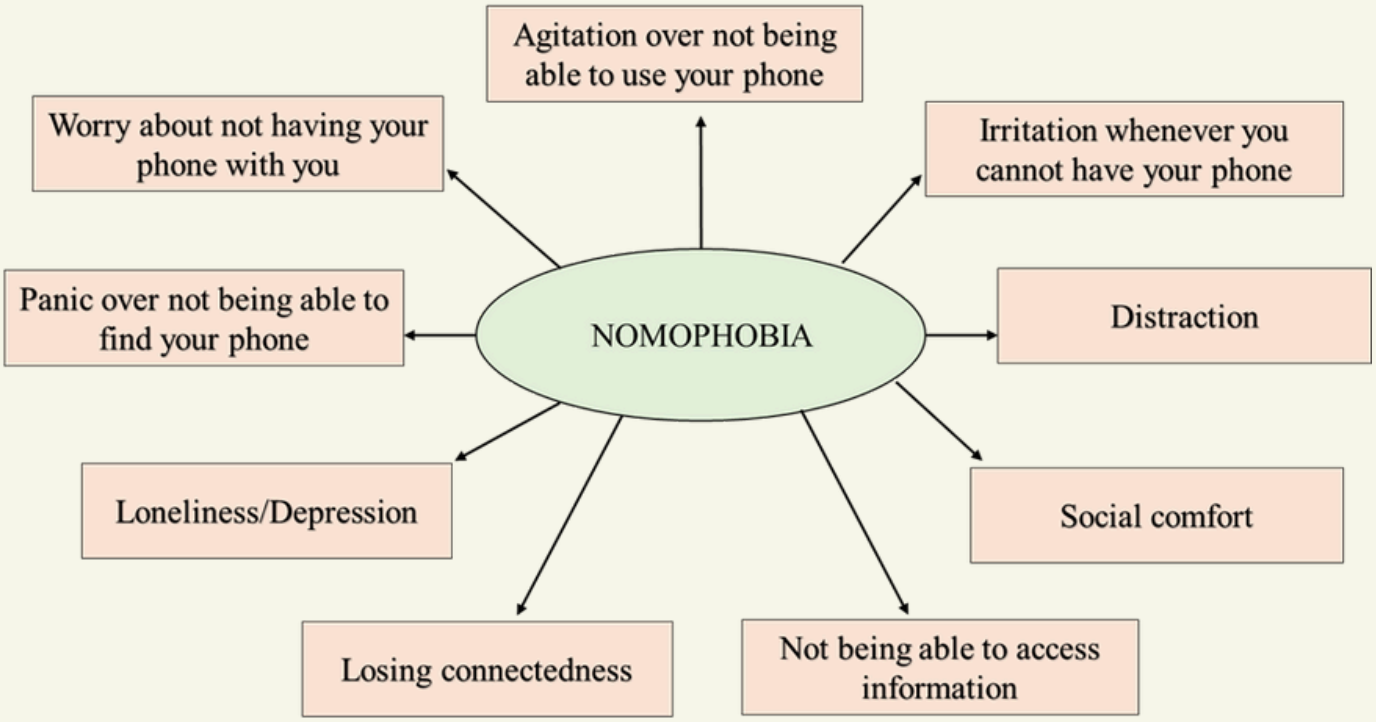
The sleep cycle is influenced by both the body's natural rhythm, known as the homeostatic sleep/wake cycle, and the circadian rhythm, which helps regulate behaviors like eating and sleeping in Humans. The circadian component is shifted by internal cycle (i.e., biological time which is different from 24 h) and is reset to 24 h by external environmental zeitgebers (e.g., the change in the temperature). The influence of age on circadian preference, adolescence is a period when the sleep cycle dramatically changes. Due to the increasing number of smartphone users and their needs, it is important to undertake investigations into the effects of smartphone use on health. While some suggest that smartphones have social connections, provide access to information, and offer entertainment, many studies highlight the negative effects of excessive use. These include sleep disturbances, anxiety, stress, low self-esteem, and depression. There is a growing concern that a lot of children and youths would encounter a psychological challenge like 'Nomophobia'.

Nomophobia is a behavioral challenge unique to smartphone users, with impacts spanning social, physiological, and physical dimensions. Those affected by nomophobia experience anxiety and nervousness, feeling compelled to constantly engage with their devices to fill a perceived void.

Since smartphone plays a vital role in the increase of nomophobia, this device offers many capabilities that have become daily essentials. Nomophobia is a growing concern as seen among youth. The prevalence of nomophobia underscores the significant risk posed by smartphone addiction, often without individuals realizing they're developing it.

Nomophobia has four stages of separation anxiety; inability to communicate, loss connectedness, inability to access information, and it is inconvenient to not have a phone on hand. Nomophobia can make a person becomes anti-social. It would be very difficult for them to make real friends in real life as they have used to make friends online. Research consistently shows a link between smartphone use and various physical and mental health issues, such as depression, anxiety, musculoskeletal problems, and sleep disturbances. However, smartphones are integral to daily activities like work, education, and entertainment. Therefore, it is important not only to utilize the advantages of the smartphone but also to reduce the negative consequences. The healthcare providers and policymakers should recognize the problem and take necessary steps in raising community awareness about smatphone and its physical and mental impact.



BEYOND THE NIGHT: HORMONAL DYNAMICS IN SLEEP AND DISRUPTION

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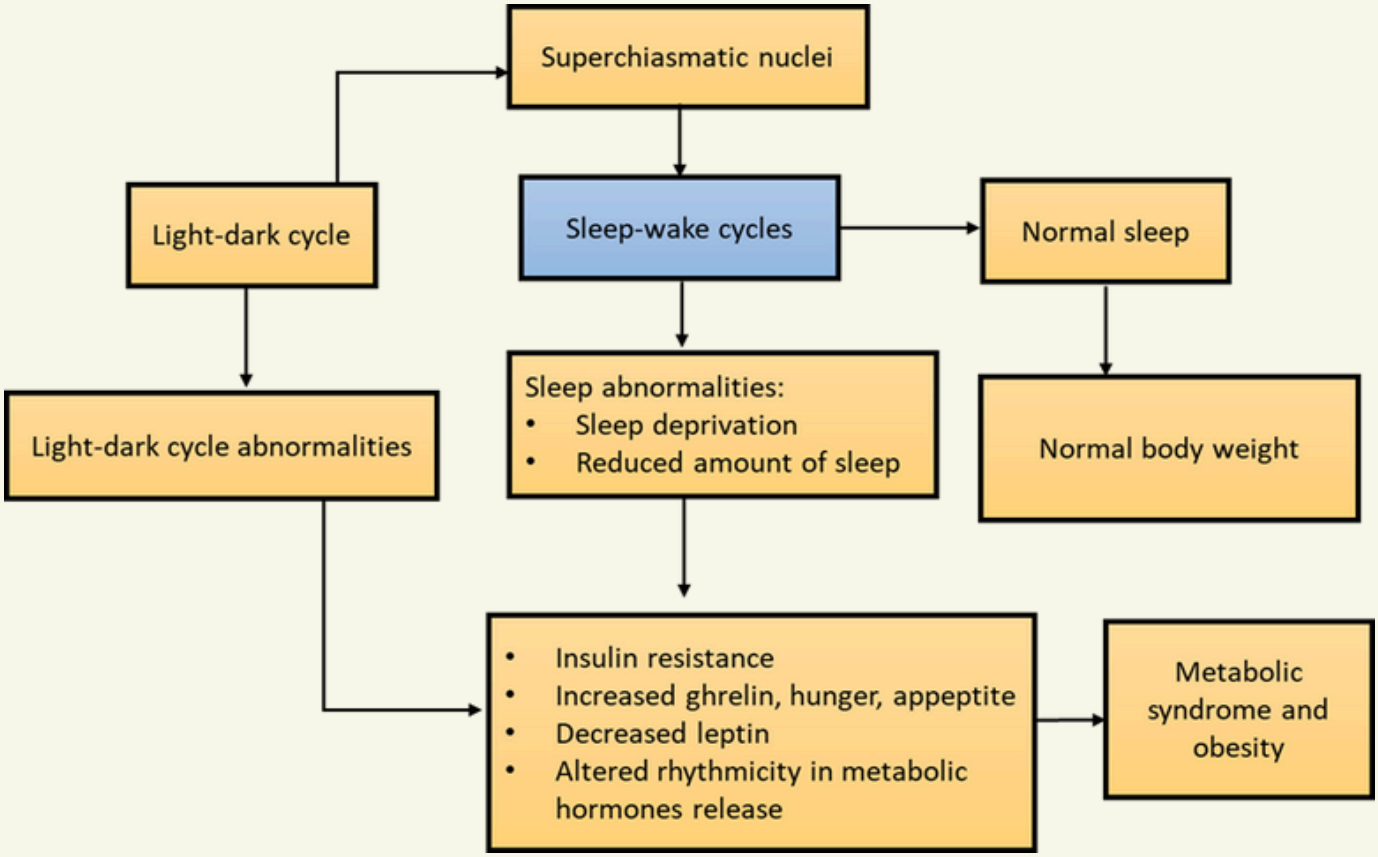
Human beings sleep for approximately one-third of their lifetime, but the endogenous mechanisms underlying sleep and its role in homeostasis remain to be fully elucidated. The circadian clock is an autonomous mechanism that prepares an organism to interact with external stimuli on cell, organ, and organism levels. The circadian system is characterized by endogenous rhythmicity and an ability to shift its timing by external factors. The suprachiasmatic nucleus (SCN), located in the anterior hypothalamus above the optic chiasm, constitutes the major site of circadian rhythm regulation. The regulation of these hormones is influenced by interactions between the effects of sleep and the intrinsic circadian system such that adverse health effects due to hormonal or metabolic imbalances may occur when the sleep cycle and intrinsic timing system are unsynchronized, the effects of sleep disturbance on hormones and metabolic function. The various hormones and metabolic processes are affected by sleep quality and circadian rhythms; such interactions are mediated by numerous clock genes. Hormones such as growth hormone, melatonin, cortisol, leptin, and ghrelin are closely associated with sleep and circadian rhythmicity, and endogenous circadian-regulating mechanisms play an important role in glucose and lipid homeostasis.

Several hormones are involved in sleep and circadian rhythmicity. Growth hormone levels are increased during sleep and peak immediately after sleep onset. Growth hormone is intermittently secreted during sleep. Melatonin, known



for its strong circadian pattern, peaks during the biological night and projects from the SCN to various regions including the pineal gland, influencing sleep regulation significantly. Melatonin administration, especially through sustained release or transdermal methods, has been shown to enhance sleep quality by reducing latency, prolonging total sleep time, and promoting better sleep maintenance. Thyroid-stimulating hormone (TSH) levels reach their highest and lowest points during the middle of the biological night and afternoon, respectively. Cortisol, another hormone with a circadian rhythm, rapidly rises during the biological night, peaking in the morning. Ghrelin and leptin play roles in appetite regulation, with ghrelin levels increasing before meals and decreasing afterward, while leptin levels rise during the biological night, reaching a peak in the morning.

Increased food intake and decreased physical activity are both major factors in the development of obesity; epidemiological studies demonstrate that worldwide obesity prevalence continues to increase. Sleep duration might also be associated with obesity development. Sleep debt in humans may increase obesity risk. Furthermore, evening cortisol concentration and sympathetic nervous system activity were increased during sleep deprivation, during which leptin levels were also at their lowest. Acute or chronic sleep deprivation may induce appetite dysregulation and raise the risk of weight gain, thereby leading to insulin resistance, glucose intolerance, and a concomitant increased risk of diabetes mellitus. Sleep disturbances and, particularly, deprivation is associated with an increased risk of obesity, diabetes and insulin insensitivity, and dysregulation of leptin and ghrelin, which negatively impact human health.

Hormones	Outcome
• Cortisol ↑	Appetite increases
• Ghrelin ↑	Appetite increases
• Leptin ↓	Appetite increases, as leptin suppresses appetite
• Insulin secretion ↓	Blood glucose levels rise, increasing insulin resistance risk
• Thyroid Hormones ↓	Metabolic rate reduces
• Growth Hormone(GH) ↓	Metabolic rate reduces, as does tissue and bone repair
• Melatonin ↑	Fatigue and sleepiness increases

SLEEP DISORDERS IN HUMAN

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Sleep is an important biological function that helps to restore the efficiency of immune, nervous, skeletal, cardiovascular, and muscular system. Our sleep/wake cycle is regulated by homeostatic sleep drive and circadian influences. The homeostatic drive, that is, the need for sleep adds up all day, reaches the zenith just before bedtime, and disperses throughout the sleep (Lack and Wright, 2007; Deboer, 2018). The circadian process involves self-sustaining 24-h rhythms of physiological activities. These rhythms govern a wide range of functions, with sleep being the most prominent. The master of these rhythms is the suprachiasmatic nucleus (SCN), which synchronizes internal processes with the external light-dark cycle. Sunlight resets the SCN daily and ensures that our internal clock stays aligned with the external environment (Lack and Wright, 2007). This alignment is necessary for healthy sleep. However, disturbances to these rhythms can lead to a variety of sleep disorders. Here's where chronobiology sheds light on the culprits behind these issues:

Ø Circadian Rhythm Sleep Disorders (CRSDs): These disorders originate directly from a mismatch between the internal sleep-wake cycle and the external environment e.g. Delayed Sleep Phase Syndrome (DSPS), where falling asleep and waking up occur later than desired, and jet lag, a temporary misalignment caused due to rapid travel across time zones. In both cases, the SCN struggles to adjust, leading to difficulty initiating or maintaining sleep (Colten and Altevogt, 2006; Cleveland Clinic Fact sheet of Circadian rhythm disorders).

Ø Shift Work Sleep Disorder (SWSD): The constant disruption to light-dark exposure throws the circadian rhythms off balance of night shift workers or rotating schedule workers. This leads to daytime sleepiness and difficulty sleeping at night (Colten

and Altevogt, 2006, Cleveland Clinic Fact sheet of Circadian rhythm disorders).

Ø Non-24-Hour Sleep-Wake Disorder (N24SWD): This disorder disrupts the natural 24-hour sleep-wake cycle, causing individuals to have sleep periods that drift later by a few hours each day (Cleveland Clinic Fact sheet of Circadian rhythm disorders).

Ø Insomnia: This disorder is characterized by delayed sleep onset, fragmented sleep, and irregular sleep-wake pattern causing desynchronization of the internal clock with external light-dark cycle (Chambe et al., 2023).

Consequences of misalignment of internal clock with external light-dark cycle:

Ø Cognitive impairment: Disrupted sleep can lead to reduced alertness, memory, and difficulty in concentration.

Ø Mood disorders: Insomnia is a significant factor for anxiety and depression.

Ø Weak Immune System: fragmented or disruptive sleep can lead to weak immune system.

Ø Chronic Diseases: Desynchronization of the internal clock has been linked to increased risk of obesity, diabetes, and heart diseases.

Below are enlisted some of the ways to resynchronize the body clock:

Ø Sunlight exposure: Get regular sunlight during the day, especially in the morning (Blume et al., 2019).

Ø Caffeine: Avoid caffeinated drinks like tea and coffee in the evening.

Ø Dim light in the evening: Avoid bright screens and blue light at least 1 hour before bedtime (Green et al., 2017).

Ø Bedtime routine: Set up a calming routine before bed to signal your brain that it is time to sleep.

Ø Consistent sleep schedule: maintain the same bedtime and wake-up time routine every day (Biggs et al., 2011).

In conclusion it could be said that sleep disorders often emerge from a disconnect between our internal clock and the external environment. By exploring the world of chronobiology, we gain a better understanding of the root causes of these issues. With the help of chronobiology, we can develop effective treatment strategies and adopt healthy habits to promote good sleep- a crucial element for our overall health and well-being.

References

- Biggs SN, Lushington K, van den Heuvel CJ, Martin AJ, Kennedy JD. Inconsistent sleep schedules and daytime behavioral difficulties in school-aged children. Sleep Med. 2011, 12(8), 780-6.
- Blume C, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and mood. Somnologie (Berl). 2019, 23(3), 147-156.
- Chambe J, Reynaud E, Maruani J, Fraih E, Geoffroy PA, Bourgin P. Light therapy in insomnia disorder: A systematic review and meta-analysis. J Sleep Res. 2023, 32(6), e13895.
- Colten HR and Altevogt BM (Eds) Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem. Washington (DC): National Academies Press (US); 2006.
- Deboer T. Sleep homeostasis and the circadian clock: Do the circadian pacemaker and the sleep homeostat influence each other's functioning? Neurobiol Sleep Circadian Rhythms. 2018, 5, 68-77.
- Green A, Cohen-Zion M, Haim A, Dagan Y. Evening light exposure to computer screens disrupts human sleep, biological rhythms, and attention abilities. Chronobiol Int. 2017; 34(7):855-865.
- https://my.clevelandclinic.org/-/scassets/files/org/neurological/sleep-disorders/fact-sheets/1-circadian-rhythm-disorders.pdf?la=en
- Lack LC, Wright HR. Chronobiology of sleep in humans. Cell Mol Life Sci. 2007, 64(10), 1205-15

TARGETING CLOCK PROTEINS TO MANAGE DISEASES: NEW TARGET FOR OLD PROBLEMS

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Rhythmic changes in physiology and behavior over the course of a day, commonly known as circadian rhythm, is one the most fundamental adaptations arising as a result of evolution. In humans, these rhythms are regulated by a transcription-translation feedback loop involving core-clock proteins: brain and muscle ARNT-like 1 (BMAL1), circadian locomotor output cycles kaput (CLOCK), cryptochrome (CRY1/2), period (PER1/2/3), RORα/β/g, and REV-ERBα/β.

Dysregulation in the rhythmic behavior of the central clock in the suprachiasmatic nucleus within the brain and peripheral clocks in the organs because of increasing lifestyle disturbances including irregular sleep-wake patterns, unhealthy dietary considerations, and sedentary behavior predisposes us to several disease pathologies.

Increased vulnerabilities to cancers, metabolic syndrome, sleep disorders, and mental health problems are known consequences of circadian dysregulation. With the increased understanding of pathways and processes regulated by core-clock proteins at molecular level, efforts have been made to regulate these downstream events by directly targeting clock proteins. Although still in its infancy, the drug discovery efforts to target clock proteins have given rise to a broader range of therapeutic targets. These efforts have yielded some promising results with the discovery of small molecule modulators for CLOCK, CRY, ROR, and REV-ERB in cell lines and preclinical models. A CRY2 selective modulator discovered in 2022 as a potential anti-glioblastoma agent, is now in Phase 1 clinical trials led by Synchronicity Pharma (Miller et al., 2022. In addition, small molecules such as CLK8 targeting CLOCK and PF670462 targeting casein kinases (CK1ε/δ), the regulators of clock protein, highlight the initial stories of drug discovery (Rasmussen et al., 2022; Doruk et al., 2020). However, great opportunities lie in optimizing these efforts, since these small molecules exhibit poor druggability properties and may show off-target toxicities (Kavakli et al., 2022; Miller et al., 2020; Kojetin et al., 2014; Uriz-Huarte et al., 2020; Amaike et al., 2020).

The power of computational tools such as virtual screening, molecular docking, and molecular dynamics simulations has been pivotal to discovering newer modulators and understanding the structural basis of experimentally discovered molecules. With crystal structure available for core-clock proteins, harnessing computational methods can pave the way for dynamics and structure-based drug discovery.

In light of this, we use computational approaches to dissect the behavior of small molecules and clock proteins at atomistic level through long time scale simulations. Understanding the mechanistic basis through atom level simulations aids current research by providing rationale while designing small molecules to target clock proteins. Recent studies have focused on understanding

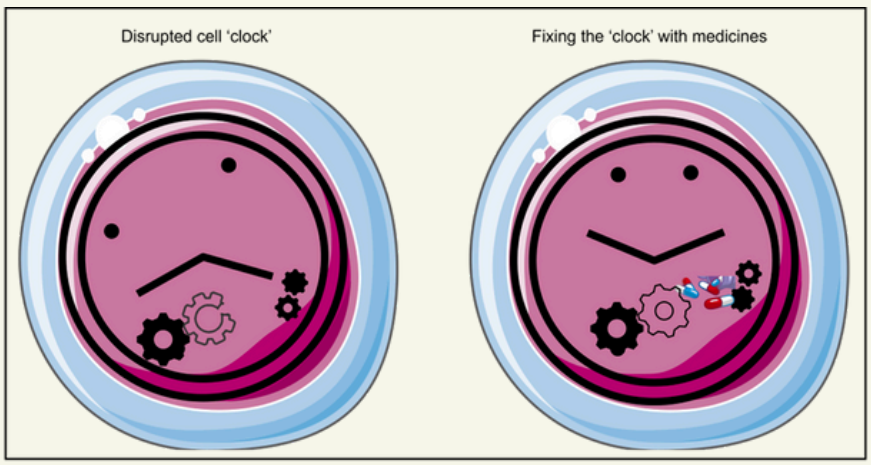
the mechanistic basis of small molecules that may act as activators (agonists) or repressors. (antagonist) of REV-ERBβ, a core-clock protein belonging to nuclear receptor protein superfamily (Burris et al., 2023; Weikum et al., 2018).

Several studies had previously reported dysregulated REV-ERB activity in diseases such as diabetes mellitus, dyslipidemia, myopathies, cancers, fatty liver disease, and Alzheimer's disease (De Meu et al., 2015; Solt et al., 2012; Gomatou et al., 2023; Welch et al., 2017; Yuan et al., 2019; Wang et al., 2015; Roby et al., 2019; Mayeuf-Louchart et al., 2017). Since the nuclear receptor family has been an active drug-discovery target, the researchers were prompt to target REV-ERB (Uriz-Huarte et al., 2020). However, the discovery of small molecule modulators was experimental, and lacked an understanding of mechanistic basis of small molecule activity. Using computational experiments, we tried to understand the structural basis of small molecule activity.

REV-ERBβ is an atypical nuclear receptor with heme as an endogenous ligand. It lacks the conserved Helix-12 in its ligand-binding domain (LBD), critical for recruiting co-activator peptide for target gene activation. Thus, REV-ERBβ could only recruit nuclear co-repressor peptide (NCoR) to transcriptionally repress downstream target genes. NCoR interacting domain (ID1/2) binding to a structurally stable LBD is central to REV-ERB activity (Mosure et al., 2021). Thus, we characterized LBD dynamics in apo, heme, and heme+NCoR-bound states.

We found that orthosteric binding pocket remained closed in absence of a ligand and heme stabilized LBD dynamics and NCoR ID1/2 peptide binding. We then compared the NCoR ID1/2 peptide binding behavior in presence of experimentally discovered small molecule modulators. The initial findings from molecular docking revealed a difference in the binding modes for agonist and antagonist molecules within the orthosteric binding pocket. We observed a differential effect of antagonist and agonist on ID peptide binding. A loss of interactions of ID1 N-terminus in presence of antagonist, and a higher fluctuation in presence of antagonist was also observed for ID1 N-terminus and ID2 peptide. In conclusion, we could identify structure specific features that resulted in small molecule activity (Srivastava et al., 2024).

Since experimentally discovered molecules faced challenges of poor pharmacokinetic profiles and non-selectivity, our preliminary results lay foundation for rational structure-based drug designing studies for REV-ERBβ. The experimental validation of optimized compounds could further the development of targeting this nuclear core-clock protein in diseases pathologies.



References

- Amaike K, Oshima T, Skoulding NS, Toyama Y, Hirota T, Itami K. Small Molecules Modulating Mammalian Biological Clocks: Exciting New Opportunities for Synthetic Chemistry. Chem. 2020 Sep;6(9):2186–98.
- Burris TP, de Vera IMS, Cote I, Flaveny CA, Wanninayake US, Chatterjee A, et al. International Union of Basic and Clinical Pharmacology CXIII: Nuclear Receptor Superfamily-Update 2023. Pharmacol Rev. 2023 Nov;75(6):1233–318.
- De Mei C, Ercolani L, Parodi C, Veronesi M, Vecchio C Lo, Bottegoni G, et al. Dual inhibition of REV-ERBβ and autophagy as a novel pharmacological approach to induce cytotoxicity in cancer cells. Oncogene. 2015 May 14;34(20):2597–608.
- Doruk YU, Yarparvar D, Akyel YK, Gul S, Taskin AC, Yilmaz F, et al. A CLOCK-binding small molecule disrupts the interaction between CLOCK and BMAL1 and enhances circadian rhythm amplitude. Journal of Biological Chemistry. 2020 Mar;295(11):3518–31.
- Gomatou G, Karachaliou A, Veloudiou OZ, Karvela A, Syrigos N, Kotteas E. The Role of REV-ERB Receptors in Cancer Pathogenesis. Int J Mol Sci. 2023 May 19;24(10):8980.
- Kavakli IH, Gul S, Turkay M. Identification of novel small molecules targeting core clock proteins to regulate circadian rhythm. Curr Opin Chem Eng. 2022 Mar;35:100730.
- Kojetin DJ, Burris TP. REV-ERB and ROR nuclear receptors as drug targets. Nat Rev Drug Discov. 2014 Mar 28;13(3):197–216.
- Mayeuf-Louchart A, Thorel Q, Delhaye S, Beauchamp J, Duhem C, Danckaert A, et al. Rev-erb-α regulates atrophy-related genes to control skeletal muscle mass. Sci Rep. 2017 Oct 30;7(1):14383.
- Miller S, Kesherwani M, Chan P, Nagai Y, Yagi M, Cope J, et al. CRY2 isoform selectivity of a circadian clock modulator with antiglioblastoma efficacy. Proceedings of the National Academy of Sciences. 2022 Oct 4;119(40).
- Miller S, Hirota T. Pharmacological Interventions to Circadian Clocks and Their Molecular Bases. J Mol Biol. 2020 May;432(12):3498–514.
- Mosure SA, Strutzenberg TS, Shang J, Munoz-Tello P, Solt LA, Griffin PR, et al. Structural basis for heme-dependent NCoR binding to the transcriptional repressor REV-ERBβ. Sci Adv. 2021 Jan 29;7(5).
- Rasmussen ES, Takahashi JS, Green CB. Time to target the circadian clock for drug discovery. Trends Biochem Sci. 2022 Sep;47(9):745–58.
- Roby DA, Ruiz F, Kermath BA, Voorhees JR, Niehoff M, Zhang J, et al. Pharmacological activation of the nuclear receptor REV-ERB reverses cognitive deficits and reduces amyloid-β burden in a mouse model of Alzheimer's disease. PLoS One. 2019 Apr 11;14(4):e0215004.
- Srivastava S, Thakur R, Srivastava A. Investigating REV-ERBβ Binding Pocket Dynamics with Implications for Rational Design of Small Molecule Modulators. bioRxiv [Internet]. 2024 Jan 1;2024.04.13.589008.
- Solt LA, Wang Y, Banerjee S, Hughes T, Kojetin DJ, Lundasen T, et al. Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. Nature. 2012 May 29;485(7396):62–8.
- Uriz-Huarte A, Date A, Ang H, Ali S, Brady HJM, Fuchter MJ. The transcriptional repressor REV-ERB as a novel target for disease. Bioorg Med Chem Lett. 2020 Sep;30(17):127395.
- Wang Y, Kojetin D, Burris TP. Anti-proliferative actions of a synthetic REV-ERBα/β agonist in breast cancer cells. Biochem Pharmacol. 2015 Aug;96(4):315–22.
- Weikum ER, Liu X, Ortlund EA. The nuclear receptor superfamily: A structural perspective. Protein Science [Internet]. 2018 Nov 25;27(11):1876–92.
- Welch RD, Billon C, Valfort AC, Burris TP, Flaveny CA. Pharmacological inhibition of REV-ERB stimulates differentiation, inhibits turnover and reduces fibrosis in dystrophic muscle. Sci Rep. 2017 Dec 7;7(1):17142.
- Yuan X, Dong D, Li Z, Wu B. Rev-erbα activation down-regulates hepatic Pck1 enzyme to lower plasma glucose in mice. Pharmacol Res. 2019 Mar;141:310–8.

Spotlight event

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