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Circadian Rhythms and Host Behavioral Manipulation: Alterations to Host Physiology and Resulting Behavioral Changes

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Abstract: **Parasite's ability to manifest host's physiological mechanisms is evident due to manipulated behavior observed via specific alterations. These alterations are achieved through various specific mechanisms which can be traced back to epigenetic modifications caused by parasitic manipulation. Some parasites show rhythmicity as their mechanism for manipulating behavior of their hosts, and this rhythmicity is attuned to their hosts. Therefore, parasites' ability to synchronize circadian rhythms with their hosts' physiology to cause alterations at genomic levels could in turn be caused by specific gene expression which may result in behavioral manipulation of the host.**

Keywords: **Circadian Rhythms; Parasitism; Host Manipulation; Biological Rhythms.**

I. INTRODUCTION

A. Chronology of Host-Parasite Interaction:

Host behavioral manipulation is one of various fascinating mechanisms addressing host-parasite interactions. Over the decades, many viable arguments have attempted to explain mechanisms by which behavioral manipulation of host can be achieved [1, 21]. However, the idea of 'extended phenotype' exhibited by parasites in order to induce a specific behavioral manipulation takes precedence, because specific alterations at genomic levels are responsible for changes and alterations in behavior within an infected physiology [9, 13, 17, 21, 25]. Hence, hosts exhibiting altered behavior due to parasitic infection is evident regardless of knowing specific mechanisms responsible for that altered behavior, and more knowledge on genomes of parasites eliciting rhythmicity would aid better explanation for such mechanisms in future [22]. Thus, it seems plausible to propose that parasitic manipulation utilizes epigenetic mechanisms to alter host's gene expression, and consequently influence host's behavior [22]. And, these specific mechanisms must be the basis for alterations with gene expressions in order to elucidate a certain behavior. And, these behavioral changes can be predicted chronologically within host-parasite interactions, where some rhythmic patterns exist within the physiology of the hosts or/and the parasites [1, 9, 11].

While mechanisms responsible for specific rhythmic patterns in various hosts and parasites may still need to unravel, the idea of entrainment, synchronizing to the circadian rhythms of the hosts' was accepted early in the 1970's [1, 9, 8, 11]. To further investigate this idea, this paper will focus on three parasitic genera, Plasmodium, Trypanosomes, and Ophiocordyceps, whose rhythmicity and synchronous activity along with alterations within their hosts has been well studied to be able to formulate plausible implications relating synchronization of circadian rhythms and alterations in host physiology at epigenetic level causing host behavioral changes [22].

B. Circadian Rhythms and a Proposed Hypothesis:

In 1973, F. Hawking proposed four ways in which the circadian rhythms of the parasites may be classified: 1) rhythms in which parasites migrate back and forth within their host body, 2) rhythms based on synchronous cell division of parasites

within their host body, 3) rhythms based on synchronous ejection of infective produces from the host body, and 4) migrating intestinal worms up and down the intestine in the host body [1]. While this classification seems viable pertaining motions of parasites within their host bodies, it lacks the foundation to relate circadian rhythms and parasites at the genomic level [1]. Classification, 1) And 4) above are based on the parasites movement within the host body, while 2) and 3) touch bases on synchronization due to parasitic growth within the host body [1]. Years later, it is clearer: parasites show rhythmic patterns in reproduction and release from their host; and these rhythms are synchronized and modulated upon environmental factors [11]. Thus, circadian rhythms are endogenous as well as regulated upon environmental cues: driven by cell autonomous transcription-translation feedback loops integrating an organism to changes in light, temperature, and other factors [1, 5, 8, 11]. Therefore, it can be hypothesized that synchronizing circadian rhythms with host physiology could be the main aspect (at epigenetic level) of behavioral manipulation to initiate physiological changes with periodicity to cause behavioral changes to better accommodate parasitism for parasites exhibiting rhythmicity [13, 17, 19, 21].

II. CIRCADIAN RHYTHMS AND PARASITISM

A. Why Should Parasites Have Rhythm?

When addressing host-parasite dynamics, circadian rhythms were thought to be crucial for better transmission for parasites (in 1970's) [1]. Then, more evidence revealed that rhythms influence host infection dynamics as well as transmission between hosts [11]. In addition, intense selective pressures of parasites to elicit a specific manifestation within the host's physiology or a vector's physiology should be confirmed to their rhythms, as their ability to infect is dependent on a certain time of the day [11]. Thus, the general concept of rhythmic patterns correlating with transmission rates, may it be dispersal of spores or dispersal of gametocytes, upon or within the host body, is a reasonable phenomenon when referring host- parasite interactions [11, 12, 17].

B. Circadian Rhythms and Peripheral Oscillators:

Environmental fluctuations are detected by an intrinsic representation of time controlled by endogenous biological clocks; and organisms relying on their environmental cues to modulate their physiological processes have adapted this system of detection [11]. Among these biological clocks are circadian rhythms, driven by cell autonomous transcription-translation feedback loops, integrated across an organism's periphery [11]. Circadian Rhythms are attuned with diel changes in light, temperature, and other extrinsic factors [8, 11]. The idea of phenotypic plasticity can better explain the notion of attunement when it comes to circadian rhythms and resynchronization (of the circadian clock) in a new environment: an organism's ability to attune and adjust their rhythms to retort their current (and less predictable) conditions [8, 11]. Along with many other behaviors, eating, sleeping and mating behaviors are controlled by circadian rhythms via peripheral oscillators: from testosterone secretion to bowel movement [8, 11].

C. Melatonin, a Circadian Hormone:

Melatonin is a circadian marker, a hormone and a regulator; a tryptophan-derived metabolite, which participates in various physiological activities [12, 19]. In addition to synchronizing the circadian rhythm, it plays a role in sleep, free radical scavenging, and immune-regulation and as an antibacterial agent [8, 12, 19]. It also performs an important role in maintaining cells' function, and due to its antioxidant properties, it has the ability to cross cell membranes [19]. Also, melatonin precursors are present within the cell biology of parasites, because melatonin is crucial and plays a role in signaling pathways and in modulating transcription factors to better sense and adapt to new environment within the host body [8, 12, 19].

During the last step of melatonin biosynthesis, melatonin precursor is methylated by an enzyme, hydroxyindole-O-methyltransperase. The activity of this enzyme yields N-acetyl-methoxytryptamine (melatonin) [19]. Hydroxyindole-O-methyltransperase is most active in the pineal gland (of the mammalian system) during night marking the dark phase [19]. Synthesized melatonin can then enter the bloodstream, which is controlled by suprachiasmatic activity which is responsible for sending light-dark information to the pineal gland [8, 19]. This illustrates how biological clocks connect and entrain with the master clock [1, 8, 19]. However, effects of melatonin on cellular functions vary among different organisms. And, its direct modulations involve regulation of cellular metabolites: second messengers, which can regulate numerous cascades responsible for cell functions [8, 12, 19]. Hence, integration between melatonin and host-parasite

interactions for modulations necessary to express 'extended genotype' to elicit 'extended phenotype' suggests variety of unique adaptations and alterations required for specific manipulation with specific rhythmicity by the parasite [13, 17, 19, 21].

III. PLASMODIUM

Malaria, which is caused by parasitic protozoan of genus Plasmodium, is one of the most infectious diseases responsible for about one million deaths annually [1, 11, 12, 19]. *Plasmodium falciparum*, the most virulent form of Plasmodium that causes cerebral malaria has been bases for many studies pertaining virulence, transmission, and cellular mechanisms to hopefully achieve a functional mechanism to eradicate the disease globally [12, 13, 19].

A. Pathology of Malaria: Life Cycle and Synchronization:

The parasite is transported between hosts by vector mosquitoes of genus *Anopheles* [1, 10, 11, 19]. To nourish its eggs, the female bites through the epidermis reaching the capillaries to feed on hemoglobin rich blood; and, one-celled malaria parasite, plasmodia escapes into the capillaries from the salivary glands of the female [1, 3, 11, 13, 19]. Then, it is transported to the liver, where each plasmodium evades into a hepatocyte to continue its life cycle and begin cell divisions. After many cell divisions, they leave the hepatocytes. Avoiding encounters by macrophages in liver sinusoids; they invade red blood cells to begin their intraerythrocytic cycle [1, 19]. This intraerythrocytic cycle marks the parasites' rhythmicity: all population of infectious parasites go through this cycle at the same time within the host body [1, 11, 12, 19]. This pattern synchronizes with the host physiology to elicit one of the many symptoms of malaria, periodicity in recurring fevers [19]. Thus, the rise in temperature due to fever is coordinated with release of parasites from infected red blood cells [1, 11, 12, 19]. This rhythmic synchronization is argued to be achieved for better transmission of the parasite [1, 11]. Because, increasing parasite cohorts after each cycle leaves the host weakened, it allows the infected hosts to be more exposed and be more susceptible to midday biting by vectors [1, 11].

B. Epigenetic Alterations and Synchronous Activity of Malaria Parasite:

The parasite can sense and adapt to its environment, which is crucial for its life cycle [12]. Thus, synchronous activity is suggested to have evolved as a strategy for the parasites to evade the immune system of their hosts [19]. Determining the genome sequence of the parasite explicates role of specific proteins and cell signaling to better understand the molecular mechanisms for the parasite's specificity [12, 13]. However, these molecular mechanisms are still undergoing research [12].

C. The role of Melatonin in Plasmodium:

Although, the mechanism for epigenetic alterations are still unknown, much research has been conducted to understand the role of melatonin in this parasite [12, 19]. Melatonin is known to play a role in the circadian cycle of the development of malaria parasite; it modulates asexual cycle of the parasite [12]. Moreover, melatonin precursors also modulate the parasite cycle to maintain synchronicity of the parasite development [12, 19]. In addition, melatonin also modulates expression of specific genes of ubiquitin proteasome system (UPS) which plays an important role in regulating development, differentiation, proliferation, cell cycling apoptosis, gene transcription, signal transduction, senescence, antigen presentation, inflammation, and the stress response [12]. Moreover, melatonin signaling can modulate gene regulation and expression [12]. Concluding, Melatonin, in Plasmodium, modulates intracellular concentrations of calcium and cAMP to ultimately regulate activities of kinases and cell cycle [19].

IV. OPHIOCORDYCEPS

A. Ophiocordyceps unilateralis: Why Make a Zombie Ant?

Known to transform and manipulate their hosts, worker or carpenter ants into zombie ants are fungal parasites of genus *Ophiocordyceps unilateralis* [9, 4, 16, 17]. The fungal parasite causes various alterations to induce a set of stereotypic behavior: leaving their nest at a different time than their regular foraging, convulsions, non-directional movements and climbing up the vegetation [17, 16]. One significant behavioral change is biting behavior, 'death grip behavior' prior to their death. This manipulated behavior is not seen in normal ants [9, 4, 16, 17]. Of various alterations, manifested by the parasite, one causes the zombie ants to express this 'extended phenotype' at a certain time of the day, this elicits synchronized manipulation by the parasite [16, 17]. And, the infected ants display the manipulated biting behavior around

noon [16, 17]. The parasite is host specific, thus requires, specific alterations to be made within the host body. These alterations (extended genotype) eventually cause the manipulated behavior (extended phenotype) [9,17]. Moreover, this 'extended phenotype' (behavioral manipulation), of course facilitates the transmission of parasites; since, once the ant is infected, its behavior alters to facilitate reproduction of the parasite and dispersal of spores [9,17].

B. Gene Expression and Zombie Ants' Manipulated Behavior:

In a mixed transcriptomics study, heads of manipulated ants were sampled after manipulated biting along with sequencing and annotating the genome of the fungal parasite [16]. And, it was found that upregulation of genes that putatively encode for proteins involved in oxidation-reduction processes and pathogenicity-related interactions [16]. Furthermore, differential expression of genes involved in apoptosis, immune and stress responses and specific behavioral manipulation are altered [16]. Thus, it is plausible to argue that this 'extended phenotype' is expressed due some alterations at genomic level within the host physiology [16, 17].

Of the 1,417 genes which are upregulated during manipulated biting behavior, those responsible for DNA binding, DNA replication, DNA repair, along with oxidation-reduction processes are overrepresented [14, 15, 16]. And, the immune related genes are down regulated in the heads of the parasites during manipulation. Moreover, carbohydrate metabolism is upregulated after the manipulated biting behavior, which suggests nutrient consumption from the host for rapid growth of fungus from within the host, forming a stalk required for further dispersion and transmission of the parasite via spores [9, 11, 16, 17].

C. Manipulated Biting Behavior Synchronized to a Certain Time of the Day:

Although, not much evidence has been found on the parasite's mechanism to manipulate the circadian rhythm of their host, manipulated biting behavior followed by their death seems to be synchronized to a certain time of the day (noon) [16, 17]. Also, the fungal parasite has a clock gene which can be representative of the complex master clock in complex organisms [8, 16, 17]. Therefore, it has been hypothesized that the circadian rhythm of the host must be manipulated by the parasite; and that expression of certain genes in the brain of their hosts must be exemplified by positive and negative feedback loops in order to control the host's peripheral body to cause behavioral manipulation [8, 14, 15, 16, 17]. For example, gene expression for metabolites such as penitrams, which are involved in modulating ion channels in neurons within the nervous system, inhibit the big potassium (BK) channels involved in passive smooth muscle contractions and neural contractions resulting in unintentional rhythmic muscle contractions within the host [4, 16].

V. TRYPANOSOMES

A. Trypanosoma brucei And Physiological Alterations of Rhythmic Patterns:

Sleeping sickness which is a disease caused by *Trypanosoma brucei*, hallmarks sleep alterations. In addition, it also causes severe disturbances in functions of nervous system which causes sensory alterations [23]. These alterations along with sleep- wake organization also exhibit rest-activity and body temperature rhythms being altered; which correlate with the time interval crucial for the parasite for neuro-invasion; invading the choroid plexus and circumventricular organs [7, 18, 22, 24]. These alterations are marked with the stage in parasite's life cycle, when it evolves from first-hemolymphatic stage to second meningo-encephalitic stage; when it crosses the blood-brain barrier in their hosts [22]. In addition, disorders of sleep pattern and endogenous rhythms in sleeping sickness have been directed towards neuro-inflammatory signaling and modulation of the immune response caused via alterations of cytokine environment [7, 11, 18, 24]. Moreover, the parasite also produces prostaglandins within the *pia mater* which induces the deregulation of sleep-wake cycles [22, 24]. However, specific time and many pathogenic mechanisms responsible for these alterations are yet to be clarified [7].

It is interesting, that although, these parasitic protozoan invades the brain parenchyma of their host's body, they only mildly alter the molecular circadian clock function but significantly dismantle the peripheral clocks, mainly in the pituitary gland, pineal gland, and spleen [7]. And, circadian oscillation of core temperature is seen within the hosts with rising temperature during the dark phase and falling during the light phase [2]. As a result, some host behavioral alterations include reduction of water consumption, food intake, and feces production [7]. Concluding, these behavioral alterations would ultimately facilitate parasitic development (life cycle) and benefit transmission rates [2, 7, 23].

B. Clock Gene Expression Altering Molecular Oscillations in Peripheral Oscillators:

Trypanosome infection causes reduced expression of *Per1-luc*, which is the clock gene in host's Central clock, the Suprachiasmatic Nucleus (SCN) within the host body. This effect is caused due to disturbed rhythmic secretion of cortisol and prolactin controlled by a hierarchy of circadian clocks within the SCN, arcuate nucleus and the endocrine gland via hypothalamic neuroendocrine regulator [20]. This ensues altered clock functions within the pituitary cells, and as a result, it alters the rhythmic secretion of associated hormones [20]. Moreover, melatonin producing pineal gland is also altered, because this results in significantly reduced amount of *clock* mRNA, transcribed clock gene. Also, the spleen is significantly affected and enlarged due to sleeping sickness, which suggest that activity of immunoactivated slpenocytes may be altered as well [20]. Therefore, the parasite affects the circadian rhythms subsequent to the SCN molecular clock altered via the molecular oscillations within the peripheral oscillators; the pituitary gland, the pineal gland, and the spleen, which are crucial for homeostatic regulation of the endocrine, immune, and sleep physiology [11, 20, 24]

C. Role of Melatonin in Trypanosoma:

As mentioned earlier, melatonin is also known as the circadian hormone responsible for many physiological activities. And, this hormone plays a crucial role when addressing manipulation of rhythmic patterns by Trypanosomes within its host's body [19, 20]. Trypanosomes can modulate the immune system by melatonin, which is crucial in controlling the parasite population [19]. Also, melatonin secretion rhythm is disturbed with reduced production within the host's body. Thus, the parasite can alter its host's sleep patterns due to decreased melatonin levels [6, 8, 19].

VI. CONCLUSION

Although, the scope of this review is to introduce reasonable implications pertaining circadian rhythms host-parasite interactions, much research still needs to take part in order to discover specific alterations caused due to manipulation. Circadian rhythms can be viewed as a common ground, where manipulating host behavior involves synchronization of rhythmic patterns and expression of specific rhythm altering genes to make an infected physiology to result in manipulated behavior [13, 17, 19, 21]. And, since these implications merge multiple disciplines, intersecting chronobiology, disease and behavioral ecology, evolutionary biology, neurobiology, and molecular biology may aid to understand how rhythms influence host-parasite interactions [9, 11, 25]. Therefore, understanding how hosts' phenotype is influenced by parasites and studying parasites may uncover yet to be explored links between the brain, immune system, and behavior [25].

REFERENCES

[1] Hawking, F. (1973) Circadian Rhythms of Parasites. *Biological Aspects of Circadian Rhythms*. (Mills, J.N.), pp. 153-187, Plenum.

[2] Berge, B, Chevrier, C, Blanc, A, Rehailia, M, Buguet, A, & Bourdon, L 2005, 'Disruptions of ultradian and circadian organization of core temperature in a rat model of African trypanosomiasis using periodogram techniques on detrended data', *Chronobiology International*, 22, 2, pp. 237-251.

[3] Rund, S, Gentile, J, & Duffield, G n.d., 'Extensive circadian and light regulation of the transcriptome in the malaria mosquito Anopheles gambiae', BMC Genomics, 14, p.

[4] de Bekker, C, Merrow, M, & Hughes, D n.d., 'From Behavior to Mechanisms: An Integrative Approach to the Manipulation by a Parasitic Fungus (Ophiocordyceps unilateralis s.l.) of Its Host Ants (Camponotus spp.)', Integrative And Comparative Biology, 54, 2, pp. 166-176.

[5] Toledo, R, Munoz-Antoli, C, & Esteban, JG 'Production and chronobiology of emergence of the cercariae of Euparyphium albuferensis (Rematoda: Echinostomatidae)', Journal of Parasitology, vol. 85, no. 2, pp. 263-267.

[6] Buguet, A, Tapie, P, & Bert, J 'Reversal of the sleep/wake cycle disorder of sleeping sickness after trypanosomicide treatment', Journal of Sleep Research, vol. 8, no. 3, pp. 225-235.

[7] Etet, PS, Palomba, M, Colavito, V, Grassi-Zucconi, G, Bentivoglio, M, & Bertini, G 2012, 'Sleep and Rhythm Changes at the Time of Trypanosoma brucei Invasion of the Brain Parenchyma in the Rat', *Chronobiology International*, vol. 29, no. 4, pp. 469-481.

[8] Sehgal, A. (2004). *Molecular biology of circadian rhythms*. Hoboken, N.J.: Wiley-Liss.

[9] Moore, J. (2002). *Parasites and the behavior of animals* (Oxford series in ecology and evolution). Oxford; New York: Oxford University Press.

[10] Goater, T., Goater, Cameron P., author, & Esch, Gerald W. author. (2014). Parasitism: The diversity and ecology of animal parasites (Second ed.).

[11] Martinez-Bakker, & Helm. (2015). The influence of biological rhythms on host–parasite interactions. *Trends in Ecology & Evolution, 30*(6), 314-326.

[12] Lima, W., Holder, A., & Garcia, C. (2013). Melatonin Signaling and Its Modulation of PfNF-YB Transcription Factor Expression in Plasmodium falciparum. *International Journal Of Molecular Sciences, 14*(7), 13704-13718.

[13] Spillman, N., Beck, J., & Goldberg, D. (2015). Protein Export into Malaria Parasite Infected Erythrocytes: Mechanisms and Functional Consequences. *Annual Review of Biochemistry, 84*, 813-841.

[14] "New Genomic Research Data Have Been Reported by Researchers at Ludwig-Maximilians-University (Gene expression during zombie ant biting behavior reflects the complexity underlying fungal parasitic behavioral manipulation)." *Life Science Weekly* 15 Dec. 2015: 1324.

[15] "Researchers at National Center for Genetic Engineering and Biotechnology Have Reported New Data on Genomic Research (Insights from the genome of Ophiocordyceps polyrhachis-furcata to pathogenicity and host specificity in insect fungi)." *Life Science Weekly* 26 Jan. 2016: 2806.

[16] De Bekker, C., Ohm, R., Loreto, R., Sebastian, A., Albert, I., Merrow, M., . . . Hughes, D. (2015). Gene expression during zombie ant biting behavior reflects the complexity underlying fungal parasitic behavioral manipulation. *Bmc Genomics, 16*, Bmc Genomics, 2015 Aug 19, Vol.16.

[17] Hughes, D., Andersen, S., Hywel-Jones, N., Himaman, W., Billen, J., & Boomsma, J. (2011). Behavioral mechanisms and morphological symptoms of zombie ants dying from fungal infection. *BMC Ecology, 11*, 13.

[18] Schultzberg, Ambatsis, Samuelsson, Kristensson, & Van Meirvenne. (1988). Spread of Trypanosoma brucei to the nervous system: Early attack on circumventricular organs and sensory ganglia. *Journal of Neuroscience Research, 21*(1), 56-61.

[19] Bagnaresi, Piero, Nakabashi, Myna, Thomas, Andrew P., Reiter, Russel J., & Garcia, Célia R.S. (2011). The role of melatonin in parasite biology. *Molecular & Biochemical Parasitology, 181*(1), 1-6.

[20] Lundkvist, G., Sellix, M., Nygård, M., Davis, E., Straume, M., Kristensson, K., & Block, G. (2010). Clock Gene Expression during Chronic Inflammation Induced by Infection with Trypanosoma brucei brucei in Rats. *Journal of Biological Rhythms, 25*(2), 92-102.

[21] Knight, K. (2013). HOW PERNICIOUS PARASITES TURN VICTIMS INTO ZOMBIES. *Journal of Experimental Biology, 216*(1), I-Iv.

[22] Adamo, Shelley Anne. (2013). Parasites: Evolution's neurobiologists. (special issue: Neural parasitology - how parasites manipulate host behavior) (Report)(Author abstract). *Journal of Experimental Biology, 216*(1), 3.

[23] Kristensson, Nygård, Bertini, & Bentivoglio. (2010). African trypanosome infections of the nervous system: Parasite entry and effects on sleep and synaptic functions. *Progress in Neurobiology, 91*(2), 152-171.

[24] Mogk, Meiwes, Shtopel, Schraermeyer, Lazarus, Kubata, Duszenko. (2014). Cyclical appearance of African trypanosomes in the cerebrospinal fluid: New insights in how trypanosomes enter the CNS. *PloS One, 9*(3), E91372.

[25] Weinersmith, K., & Faulkes, Z. (2014). Parasitic Manipulation of Hosts' Phenotype, or How to Make a Zombie—An Introduction to the Symposium. *Integrative and Comparative Biology, 54*(2), 93-100.