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Research on genetic regulation of sleep

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Abstract. Sleep is the most vital function of mammals to maintain energy homeostasis. For years, the mechanism behind how sleep is regulated has been studied, and several genetic pathways had been identified as the key to encoding the circadian rhythms to enable the mammalian sleep and wake cycles. This paper explains the mechanisms behind the PER, CRY, CLOCK, and BMAL1 pathways, which play a central role in manipulating the function of the circadian clock. Other pathways, such as the DEC1/2 genes, interact with the circadian clock genes to form negative feedback loops to further control the circadian rhythm pathway and directly regulate sleep through orexin. Mutations occurring in these pathways could potentially cause conditions such as narcolepsy, restless leg syndrome, insomnia, sleep apnea, delayed sleep phase syndrome (DSPS), and advanced sleep phase syndrome (ASPS). These conclusions are based on previous studies and experiments that identified these pathways. While recent studies have shed light on the mechanisms of the PER, CLOCK, BMAL1, and DEC genes in regulating sleep and circadian rhythms, there is still much to discover. The intricate interactions and genetic pathways involved in sleep regulation are not yet fully understood. Further research in this field may uncover new insights into the genetic basis of sleep and provide avenues for developing interventions to address sleep disorders.

Keywords: genetic regulation, sleep disorders, circadian system.

1. Introduction

Sleep is one of the most crucial functions of animals' bodies to maintain everyday functioning. Humans spend around a third of their lives in sleep every night. As past studies have indicated, sleep promotes memory consolidation, energy conservation, glycogen storage, waste protein and metabolites cleanse, and many more that are still unknown to us. Essentially, sleep helps the brain to function properly by restoring necessary energies needed and releasing unnecessary wastes. Sleep is regulated by the collaborative functioning of the human circadian system and homeostasis system. Humans sleep at night time and stay awake during day time due to the photoreceptive functioning of the ganglion cells, which sends signals to the SCN cells to synchronize the circadian rhythms with external factors. Many other pathways function together to cause sleep, including the reticular activating system, locus coeruleus, basal forebrain, and many more, in which they interact with each other to be inhibited or activated to regulate sleep or wakefulness. Many sleep disorders were identified by past researchers as various environmental factors and genetic mutations that cause disorders such as insomnia, sleep apnea, movement disorders during sleep, and narcolepsy [1]. These are primarily caused by the dysfunctioning of various possible components of the pathways regulating sleep. Which provides evidence that genetic expression is the key to regulating sleep. On a molecular level many proteins and receptors including

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PER, CLOCK/BMAL1 and DECs play a major role in the regulation of sleep by the circadian system and the homeostasis system [2]. The genes behind sleep regulation pathways encode for the complexed sleep system. This paper provides an overview of the significance of genetic regulation of sleep and the mechanisms of sleep regulation, which signifies the impact of sleep homeostasis through genes as well as disorders that could potentially be caused by the genetic mutations

2. Circadian genes

2.1. PER, CLOCK, BMAL1 gene mechanism

On Earth, most organisms are adapted to the circadian rhythms that are biologically synchronized with the 24-hour revolution of the planet. Organisms have this internal clock to regulate their behavior and health based on daylight and darkness. Genetic expression on a molecular level is fundamental to understanding the circadian rhythm. The circadian clock cycle in mammals begins in the morning with the clock and BMAL1 protein complex activating the Period (PER) and CRY mRNA transcription. These mRNAs are then transported to the cytoplasm during the day and bind with the ribosome to translate the genetic codon of PER and CRY mRNA into proteins. The proteins encoded, PER1, PER2, PER3, CRY1, and CRY2 are stored and accumulated in the cytoplasm in the latter daytime. The presence of casein kinase 1 (CK1) combines all possible combinations of PER and CRY complexes with CK1 as CK1 phosphorylates PER proteins [3]. The phosphorylation of PER proteins occurs in the evening, which enables the trimeric complex to be nuclear localized as it is able to enter the nucleus and accumulate in the cell nucleus. Due to the increasing concentration of the trimeric complex in the suprachiasmatic cell nucleus, this complex binds with the Clock and BMAL1 protein complex, which is the activator of the PER and CRY genes. The trimeric complex acts as the repressor of the Clock and BMAL1 promoters, causing the inhibition of the Per and Cry genes. As the Per and Cry mRNA and protein concentrations decrease due to their short-lived nature, the Clock and BMAL1 promoter would express the PER and CRY genes again, thus repeating another 24-hour cycle [4]. A secondary TTFL pathway regulates the presence of the BMAL1 protein. The repression of the BMAL1 protein process occurs as REV-ERBα binds to the retinoic acid-related orphan receptor response elements (RORE) to repress the expression of BMAL1. And the BMAL1 expression initiates as RAR related orphan receptor alpha (RORα) binds to RORE to promote the expression. This process is rhythmically synchronized with the outside environment's cues, as RORα concentration peaks at dusk and REV-ERBα concentration reaches its peak at dusk. This ensures that BMAL1 expression will peak around dusk time and minimize around dawn time. As the BMAL returns back to the SCN after synthesis, the increasing concentration of BMAL would increase the PER and CRY expression, therefore continuing the cycle [5].

2.2. Mutation

Mutations in the PER, CLOCK, and BMAL1 pathways could cause significant sleep disorders. As mutations occur in the PER, CRY, Clock, or BMAL1 genes, potential risks of extending and shortening sleep could occur, as well as abolishing circadian rhythms. The resulting sleep disorders include delayed sleep phase syndrome (DSPS) or advanced sleep phase syndrome (ASPS). For instance, the study in the human PER3 gene indicates that the mutation of PER3 gene nucleotides would significantly alter the amino acid components, thus affecting the CK1ϵ phosphorylation of PER3. The altered PER3 phosphorylation would then induce a significant alteration in the circadian cycle length as the heterodimers that the PER3 protein forms with PER1/2 and CRY1/2 forms are affected, which causes changes in the inhibition in the mediated transcription of CLOCK and BMAL1 and this eventually leads to the delayed sleep phase syndrome indicated by the study [6]. Mutations in the PER, CLOCK, and BMAL1 pathways could cause significant negative effects regarding the sleep cycle.

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3. Sleep duration genes

3.1. DEC1/2 gene mechanism

Sleep is a complex mechanism that is regulated by many different factors and pathways within humans. One pathway that contributes to sleep duration is the DEC1/2 gene pathway. The DEC1/2 gene regulates and has effects on several pathways, including orexin expression and circadian rhythm regulation. DEC genes are initially expressed responsively to light as they are produced in the SCN and entrained by the circadian rhythms. The DEC proteins are highly expressed during the middle of the day corresponding to the maximum expression of CLOCK and BMAL1 genes during the middle of the day due to the DEC effects on CLOCK and BMAL1 expression, and that also alters the PER gene expression. Prior studies have shown that DEC1 expression is light-induced from 20:00 to 4:00 but does not significantly change if light is given at any other time of the day. This demonstrates the circadian entrainment of DEC1 expression in mammals, which is directly modulated by the retinohypothalamic tract that has glutamate, a neurotransmitter, to increase the calcium ion concentration in the intracellular region. As calcium concentrations increase the cAMP-responsive element binding protein (CREB) activation is turned on, which then expresses the DEC1 gene and the PER1 gene, as they both have a cAMP responsive element (CRE) upstream promoter binding site for CREB. However, the DEC2 gene is not induced by light, as shown by the study. The DECs are also upregulated by the CLOCK and BMAL1 heterodimers, as PER expression initially produces BMAL1, which then causes DEC genes to be expressed as BMAL1 binds to the E box promoter region [7].

DEC 1 and DEC 2 proteins have multiple effects on the mammal sleep cycle and duration. Because the DEC proteins prevent the PER gene from being transactivated, they produce a negative feedback cycle with the PER, BMAL1, and CLOCK gene pathways. This cycle of feedback is subsequently closed by the first stimulation of the PER and BMAL1 proteins. The DECs also have significant effects in the peripheral pathways as the rhythmic expression of DECs in many peripheral tissues have significant physiological effects to mammals. Additionally, the DEC2 gene also modulates orexin expression. This process plays a crucial role in mammal sleep regulation since orexin A and orexin B, which are enriched in the hypothalamus, directly cause arousal in mammals. In the prior studies, DEC2 and DEC2 mutations had been tested, and as a result, researchers hypothesized that DEC2 protein binds to E12 and MyoD1 in the orexin promoter region. This promotes the expression of orexin, which causes wakefulness. As a conclusion, DEC2 regulates the orexin signaling pathway, however, the transcriptional factors and the DEC2 orexin pathway are still limited in our current study [8].

3.2. Mutations

Mutations in the DEC genes would directly result in abnormalities in the circadian rhythm. This is due to the abnormality in PER gene suppression, which would cause delayed sleep phase syndrome (DSPS) or advanced sleep phase syndrome (ASPS). The reported short sleep duration linked to the DEC2 amino acid mutation P385R confirms this [9]. Furthermore, a mutation in DEC genes would also alter mammalian metabolism. DECs play a crucial role in lipid metabolism regulation as they inhibit lipogenesis in the liver by repressing the lipogenic gene regulator, Srebp-1c, transcription. As a result, this alters the lipid storage level in the liver, which would greatly impact the lipid metabolism of mammals [10].

4. Conclusion

Sleep is a vital physiological process regulated by complex genetic pathways and interactions. The PER, CRY, CLOCK, BMAL1, and DEC genes play crucial roles in the regulation of sleep and circadian rhythms. The circadian clock cycle involves the activation and repression of these genes, leading to the oscillation of sleep-wake patterns. Mutations in these pathways can disrupt the normal sleep cycle and result in sleep disorders such as insomnia, sleep apnea, restless legs syndrome, and various circadian rhythm disorders. The PER, CRY, CLOCK, and BMAL1 pathway governs the core molecular mechanism of the circadian clock. These genes encode proteins that form complexes and regulate the

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expression of other clock genes, thereby controlling the oscillation of sleep-wake patterns. Dysfunctions in this pathway can lead to disturbances in the timing and duration of sleep. The DEC1/2 genes interact with the circadian clock genes and have multiple effects on sleep duration. They contribute to the regulation of orexin expression, a neuropeptide involved in arousal and wakefulness. Mutations in the DEC genes can disrupt the circadian rhythm and affect sleep duration. Understanding the genetic regulation of sleep has important implications for improving sleep health and addressing sleep disorders. With a better understanding of the genetic mechanisms underlying sleep, it may be possible to develop targeted therapies and interventions for individuals with sleep disorders. Additionally, identifying genetic markers associated with sleep disorders could aid in early diagnosis and personalized treatment approaches. In conclusion, the study of genetic regulation in sleep provides valuable insights into the fundamental mechanisms of sleep-wake regulation. Continued research in this field holds promise for advancing our understanding of sleep disorders and developing effective interventions to promote healthy sleep patterns and overall well-being.

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