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Gut Microbiota in Circadian Rhythm and Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD) causes a significant burden in society. However, the underlying pathology is still poorly understood. In addition to its classic suggested pathways, recent research also indicated that neuroinflammation may be a potential trigger of AD. Meanwhile, rhythm disruption may stimulate a systemic pro-inflammatory state. According to clinical studies, the altered gut microbiota composition has been reported in AD as well as sleep-deprived patients. These changes include the increased pro-inflammatory microbiota proportion, which has been found to induce neuroinflammation, neurodegeneration, β-amyloid (Aβ) production, and accumulation that may eventually lead to AD progression. Therefore, changes in gut microbiota have been suggested to be a potential linkage between rhythm disruption and AD.

Keywords: gut microbiota, neuroninflmmation, Alzheimer's Disease, circadian rhythm

1. Introduction

The main composition of human gut microbiota is bacteria and fungi [1]. Its components can be influenced by the host's genetics, lifestyle, and drug usage. Normally, these bacteria have a symbiotic relationship with us, affect our energy balance, and protect us against pathogen colonization [2]. The main components of the gut microbiota are gram-positive bacteria such as Firmicutes and Actinobacteria and gram-positive bacteria such as Bacteroidetes and Proteobacteria. Both of them are crucial for our immune function [3]. The gut microbiota responds to intestinal regulation and gut epithelium integrity. Therefore, when microbiota dysbiosis, an imbalance of gut microorganisms, occurs, the body may live in a systemic pro-inflammatory state and lead to disease [3]. Meanwhile, as gut microbiota also have an essential influence on blood-brain barrier (BBB) integrity, they have been suggested to stimulate neuroinflammation, which in turn affects the deposition of Aβ [4].

Alzheimer's disease (AD) is a neurodegenerative disease that is characterised by a steadily declining capacity for memory, thinking, and daily functioning [5]. As a significant global public health issue that has been identified by the World Health Organization, It contributes to 60-70% of dementia cases, which will influence approximately 152 million people by 2050 [6]. According to the understanding now, the two main pathologies of AD are the β-amyloid (Aβ) plaques accumulation and neurofibrillary tangles (NFTs) [6]. However, the inflammatory response has now been observed in several studies of AD patient samples' postmortem tissues and preclinical model systems [4]. As an essential immune organ, the gut microbiota has been suggested to trigger systemic, especially neuroinflammation, via releasing pro-inflammatory cytokines, which might lead to AD onset [6].

Circadian rhythm is the alterations in an organism's body, mind, and behaviour over 24 hours [5]. Nowadays, the essential regulatory role of circadian rhythm in various human diseases has been identified; for example, inadequate sleep has been suggested as another public health issue to promote AD progression [6]. Meanwhile, a significant amount of research has been done in both animal and human trials on the impact of circadian rhythm on gut microbiota. For example, one animal study reported that circadian disruption could increase lipopolysaccharide (LPS) production and gut permeability [6], resulting in neuroinflammation and promoting the development of neurological disorders like AD.

However, the link between circadian rhythm dysregulation and AD through the action of gut microbiota has yet to be established, and there is a lack of sufficient studies. This study aims to investigate how circadian rhythm is involved in AD progression through manipulating gut microbiota composition, contributing to understanding AD pathology and clinical prevention and even treatment of AD.

2. The Role of Gut Microbiota in Circadian Rhythm Disruption and Alzheimer's Disease

2.1 Neuroinflammation

2.1.1 Changes in Gut Microbiota Lead to Systemic Inflammation

The human microbiota is the commensal microorganisms that coexist in our bodies both pathogenically and symbiotically [7]. This microbiota has been proven essential in regulating body health and disease [8].

As the most critical human immune organ, the human gut contributes up to 80% of the body's immune function [8] and controls numerous immune cells. Therefore, the gut microbiota alteration, such as the increased phylum Bacteroidetes, a class of LPS-containing gram-negative bacteria [9], may trigger the release of proinflammatory cytokines and neurotoxins, increase intestinal permeability and active the innate as well as adaptive immune systems [9]. According to clinical research, this alternation would lead to systemic inflammation [8], which may disrupt the brain's immune system and stimulate AD development. [8].

The gut microbiota-host immunological interactions may control brain immunity and functions, including neuronal development, neurotransmission, CNS immune activation, BBB integrity maintenance, and microglia and astrocytes' maturation, differentiation, and activation [9].

2.1.2 Linkage Between Alzheimer's Disease and Neuroinflammation

In the brain, in response to infections [10], microglial cells bind with lipopolysaccharide (LPS) [11], which is released by gut microbiota and has been seen in the neocortex and hippocampus of AD patients [11]. Following this, the cells produce a variety of cytokines and chemokines via myeloid differentiation factor 88 (MyD88) and nuclear factor kappa beta (NF-κB)-dependent signalling pathways. Thus, proinflammatory miRNA-146a and miRNA-155 levels are raised upon activation of NF-κB signalling, downregulating the production of complement factor H, triggering the immune system, causing neuroinflammation, and contributing to AD development [11].

Additionally, astrocytes contribute significantly to neuroinflammation [12]. Normal astrocytes preserve the integrity of the central nervous system by regulating blood circulation in the cerebrum, maintaining the blood-brain barrier, and adjusting neuron or nutrient transmission [12]. Nonetheless, it has been shown that aberrant astrocytes in AD patients' brains differ in shape, protein makeup, gene expression, and activities [13]. On the one hand, astrocytes triggered by Aβ deposit may result in upregulation of cytokines [14], and more recently, astrocytes have been demonstrated to promote A1 proinflammatory phenotype in microglia, which can lead to neuronal cell death and further neurodegeneration [14]. However, aberrant microglia lose their ability to phagocytose, which lowers the level of Aβ phagocytosis and causes Aβ buildup, both of which advance AD [15].

2.2 Circadian Rhythm Disruption

2.2.1 Circadian Rhythm Deprivation Influences Gut Microbiota Composition

Previous research has investigated the factors that may alter the composition of the gut microbiota., such as host genetics, age, and antibiotic usage [16]. Despite these, modern health issues such as sleep disturbance have recently been suggested to alter the gut microbiota composition.

Better sleep quality could improve gut microbiome diversity and the proportion of anti-inflammatory gram-positive bacteria such as Blautia [16]. Meanwhile, both short- and long-term poor sleep quality increases the number of inflammatory gram-negative bacteria such as Prevotell. Similarly, Smith et al. showed that sleep efficiency positively affects the gut microbiota composition. Meanwhile, decreased inflammatory cytokines such as IL-6 levels have also been observed in humans with better sleep quality [17], demonstrating circadian rhythm's potential role in neuroinflammation and subsequent AD progression by changing the gut microbiota composition. However, as these studies are mainly observation studies with small sample sizes and rely on self-reported methods, more random controlled trials are needed to investigate the influence of circadian rhythm on gut microbiome composition.

Additionally, the effects of sleep deprivation and gut microbiome modification have been the focus of numerous animal research. In the study by Aidy et al., the number of particular bacteria was linked to short-term sleep deprivation even though there were no noticeable shifts in the composition of the mice's gut microbiota [18]. Another study showed that sleep disruption in rats could negatively impact their gut microbiota composition, such as an elevated Firmicutes: Bacteroidetes ratio, which may induce proinflammatory status [18]. However, due to the variation of the method between studies, the results are not stable as the changes in both human and mouse microbiota showed high resistance to sleep deprivation in a study done by Zhang et al. [18].

2.2.2 Circadian Rhythm Dysrugulation and Alzhei-

mer's Disease

As a significant social issue, sleep deprivation has also been linked with several neurodegenerative diseases such as AD [19]. Recent studies have reported circadian rhythm disruption in preclinical, mild and moderate to severe [19] AD patients through analyzing the behavioural markers. Although rhythm dysregulation in preclinical AD patients has been linked to ageing instead of AD pathology [20], the overall finding is that the abnormal circadian rhythm is associated with AD, especially in moderate to severe cases. However, these studies are observation studies that only cover a small sample size; thus, the underlying mechanism between circadian rhythm disruption and AD is still missing.

Sleep is necessary for the brain's removal of metabolites, including Aβ, because it increases the fluid exchange between the interstitial fluid (ISF) and the cerebrospinal fluid (CSF), the sleep deprivation resulting from circadian rhythm dysregulation may be a potential trigger of Aβ accumulation and subsequently neuroinflammation and neurodegeneration, which ultimately lead to AD [20]. To study this hypothesis, both animal and clinical trials have been done. For example, Kang et al. [18] have found that sleep deprivation could stimulate Aβ levels significantly in mice models. Meanwhile, clinical research discovered that in healthy persons, a single night of inadequate sleep could accumulate Aβ [18]. Therefore, even if the disturbance of circadian rhythm has not been proven to have a role in AD pathogenesis, it remains a potential factor that may increase the risk of neurodegeneration and neuroinflammation, which may ultimately lead to the advancement of AD.

2.3 Gut Microbiota in Circadian Rhythm Disruption and Alzheimer's Disease

According to previous research, insufficient sleep may adversely impact the composition of the human gut microbiota by elevating pro-inflammatory bacteria and lowering anti-inflammatory bacteria [19]. These alterations may result in inflammation throughout the host body, including the brain since intestine mucosal lymphoid tissue is the most vital component of the human immune system [18]. As a result, the blood-brain barrier (BBB) integrity disruption may allow LPS passage, which triggers neuron cells to produce cytokines and chemokines and ultimately leads to neuroinflammation and neurodegeneration [19]. Similarly, circadian rhythm disruption might also increase the pro-inflammatory gut microbiota, further stimulating neuroinflammation and Aβ deposition [19]. As a result, it would even heighten brain immune cell response [20]. In particular, astrocytes tend to change phenotype, induce neuronal cell death and further neurodegeneration [20]. Meanwhile, the dysfunctioned microglia impairs brain Aβ clearance and stimulates Aβ accumulation, contributing to AD progression [20].

AD could result from gut microbiota-induced neuroinflammation, and disruption of rhythm might change the composition of the gut microbiota in a way that promotes inflammation in the brain. Therefore, the gut microbiota maybe the potential interaction factor between AD and rhythm disturbance. Based on this relationship, consuming some gut microbiota-beneficial agents may be a potential prevention or treatment method for circadian rhythm disruption, neuroinflammation and further AD. Prebiotics, for instance, consist primarily of dietary fibre components and have been proposed to decrease neuroinflammation by inhibiting the production of pro-inflammatory cytokines and increasing the production of anti-inflammatory cytokines, prevent cognitive function damage, and further Alzheimer's Disease both in humans [21] and animal studies [22]. Besides, probiotics showed similar effects when used in elderly patients with memory complaints to maintain cognitive function [22]. Therefore, more research is needed to investigate whether these supplements contribute to public health management.

3. Summary

Based on current understanding, the link between circadian rhythm disruption and AD through the action of gut microbiota has been suggested. However, more animal and human studies are needed to further understand this pathology. Further research could focus on how gut microbiota interact with circadian rhythm and AD. Clarifying this potential relationship would ultimately contribute to clinical prevention and even AD treatment.

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