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THEORETICAL REVIEW

The shift work and health research agenda: Considering changes in gut microbiota as a pathway linking shift work, sleep loss and circadian misalignment, and metabolic disease

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SUMMARY

Prevalence and impact of metabolic disease is rising. In particular, overweight and obesity are at epidemic levels and are a leading health concern in the Western world. Shift work increases the risk of overweight and obesity, along with a number of additional metabolic diseases, including metabolic syndrome and type 2 diabetes (T2D). How shift work contributes to metabolic disease has not been fully elucidated. Short sleep duration is associated with metabolic disease and shift workers typically have shorter sleep durations. Short sleep durations have been shown to elicit a physiological stress response, and both physiological and psychological stress disrupt the healthy functioning of the intestinal gut microbiota. Recent findings have shown altered intestinal microbial communities and dysbiosis of the gut microbiota in circadian disrupted mice and jet lagged humans. We hypothesize that sleep and circadian disruption in humans alters the gut microbiota, contributing to an inflammatory state and metabolic disease associated with shift work. A research agenda for exploring the relationship between insufficient sleep, circadian misalignment and the gut microbiota is provided.

Introduction

The prevalence of metabolic disease (incorporating obesity, type 2 diabetes (T2D) and metabolic syndrome) is increasing globally [2–4]. In particular, overweight and obesity have received significant attention, as excessive weight gain poses considerable economic and social burdens. A staggering 1.9 billion adults (39% of the global adult population) are estimated to be overweight, with 600 million (13%) of these individuals also meeting the criteria for obesity [3,5]. This burden contributes to a raft of non-communicable diseases, including cardiovascular diseases, diabetes, musculoskeletal diseases, sleep apnea, and in some instances, cancer [5]. Financial costs are escalating, with overweight and obesity responsible for an estimated 0.7–9.1% of total health care expenditures [6]. The relationship between sleep loss and metabolic disease is particularly pertinent for individuals who frequently experience altered sleep opportunities. As a consequence of our evolving 24/7 society, the prevalence of shift work is increasing [7]. While shift work meets societal needs, the health implications for shift workers are concerning. Shift work is associated with a high incidence of metabolic disease [8–11]. Shift workers also report disturbed sleep and impaired waking functioning, including trouble initiating sleep, shorter sleep durations and daytime sleepiness [12,13]. With an estimated 20% of the Western workforce engaged in shift work [7], understanding the relationship between shift work and metabolic disease is important for managing the rising prevalence of metabolic disease burden in shift workers.

This theoretical review will outline a proposed pathway linking shiftwork with metabolic disease via disruption to the gut microbiota. It will first consider the evidence linking disrupted gut microbiota with metabolic disease, as well as the relationship between stress and the gut microbiota. Evidence of sleep and circadian misalignment as physiological stressors (which could

Abbreviations: GLP-2, glucagon-like peptide-2; IFN-γ, interferon gamma; T2D, type 2 diabetes; TNFα, tumor necrosis factor alpha.

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Glossary of terms

Gut microbial dysbiosis	disruption of the balance of healthy and unhealthy bacteria in the gut. In the context of this article, this is predominantly as a consequence of psychological or physiological stress
Gut microbiota	refers collectively to the population of microbes residing in the intestinal tract. Composition of the gut microbiota varies between individuals, but the overarching major phyla in the human gut microbiome are Bacteroidetes and Firmicutes [1]
Metabolic disease	a collection of health conditions associated with impaired metabolic dysfunction. Within this review, these include overweight, obesity, metabolic syndrome and type 2 diabetes (T2D)
Pathobionts	microbes within the gastrointestinal tract which have the potential to cause harm to the host (in the context of this review, the human subject)
Shift work	any occupational routine characterized by work outside the 0900-1700 window

potentially disrupt the gut microbiota) is subsequently presented, before an overview of the literature linking sleep loss with metabolic diseases that are also associated with disruption to the gut microbiota. The proposed mechanistic link between sleep, circadian disruption and disruption to the gut microbiota is explored with an overview of bacterial translocation and inflammation. Finally, a new agenda for shift work - gut - health research is proposed to develop an evidence base for managing health risks associated with shift work and metabolic disease.

Changes to the gut microbiota are linked with metabolic disease

The gut microbiota play a key role in health and wellbeing [14]. Nutrient absorption, metabolism and storage, and establishment and maintenance of healthy immune and metabolic function all require input from the gut microbiota [14]. The gut microbiota are influenced by a number of factors that have only recently been identified. Factors such as age [15], diet [16], and metabolic disease [17] are associated with alterations in gut microbiota composition and function.

Early work in mouse models found that genetically obese mice show a 50% decrease in abundance of Bacteroidetes, and a relative increase in Firmicutes when compared with lean counterparts [18]. This finding was subsequently confirmed in obese human subjects [19]. Additional studies support a correlation between declines in Bacteroidetes in obese versus lean human adults [20,21], while also identifying increased proportions of *Lactobacillus* in obese subjects [20] and overall significantly decreased diversity in obese versus lean subjects [21]. The relationship between obesity and Firmicutes remains unclear. The proportions of Firmicutes after gastric bypass in obese subjects decreased [22] but in other studies, no significant difference was reported between obese and lean subjects [16,21]. Fecal transplant studies provide the most compelling evidence that microbiota play a role in development of obesity. Specifically, fecal transplant from obese to non-obese mice induced obesity in recipient mice independent of changes in diet [19]. Further support that the microbiota play a role in development of obesity comes from findings that germ-free mice without a microbiota have less total fat mass compared to wild-type mice [23] and that germ-free mice did not develop diet induced obesity [24].

The substantial influence of the gut microbiota on human obesity is further highlighted by findings from obese versus lean twin studies. When Ridaura and colleagues [25] transplanted gut microbiota from human twins with differing body mass profiles (one obese, one lean) into germ free mice, the recipient mice adopted the adipose profiles of the donor (i.e., mice receiving gut microbiota from obese twins demonstrated greater body mass and adipose gains than those receiving gut microbiota from lean twins). The profoundly different gut microbiota in the donor twins highlights two key concepts: 1) that environmental factors (such as diet) have a greater role than genetics in composition of the gut microbiota, and 2) that gut microbiota strongly influence aspects of weight gain, and the subsequent disease cascade associated with obesity.

There is also evidence of a relationship between disruption of gut microbiota and both T2D and metabolic syndrome. Larsen et al. [26] compared gut microbiota in human adults with and without T2D and found Bacteroidetes and Betaproteobacteria were elevated, while proportions of Clostridia were significantly lower in subjects who met T2D criteria compared to non-diabetic subjects. Significantly decreased proportions of Firmicutes were also present in T2D compared with non-diabetic counterparts. Elevated plasma glucose concentrations are a diagnostic feature of T2D [27] and there was a tendency for a decline in Clostridia, from the Firmicutes phylum, with increasing plasma glucose levels in patients with T2D [26]. Subsequent research from Qin et al. [28] has provided preliminary support for the notion that the gut environment of individuals with T2D reflects gut microbial dysbiosis. This was characterized in the T2D subjects by decreased prevalence of butyrate-producing bacteria. Butyrate is associated with good health and is a main energy source for colonic epithelium, a critical mediator of the inflammatory response in the colon, and regulator of fat storing gene (FFA3) expression in adipocytes [29]. The T2D patient gut microbial environment also shows dysbiosis, increased prevalence of opportunistic pathogens (in a pattern similar to what is seen in patients with colorectal cancer, and in ageing samples), and increased oxidative stress [28]. The impact of gut microbiota on metabolic syndrome is similarly pronounced [30], as is expected given the overlap in diagnostic criteria with obesity and T2D. Collectively, the literature to date provides evidence of a relationship between gut microbial dysbiosis and metabolic disease.

Less is known about how environmental factors such as sleep and circadian disruption influence the gut microbiota and related metabolic dysfunction. This will be an important avenue of future inquiry as there is emerging evidence of a causal relationship between microbial dysbiosis, inflammation and disease, including metabolic dysfunction.

Stress disrupts the gut microbiota

Physiological and psychological stress have the capacity to disrupt the gut microbiota, negatively influence gut permeability, and contribute to poor health. In a healthy gut environment, the epithelial barrier is a well-maintained structure designed to restrict the impact of pathobionts, and promote and support anti-

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