

Peripheral circadian misalignment: contributor to systemic insulin resistance and potential intervention to improve bariatric surgical outcomes

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Submitted 19 May 2016; accepted in final form 26 July 2016

Kunze KN, Hanlon EC, Prachand VN, Brady MJ. Peripheral circadian misalignment: contributor to systemic insulin resistance and potential intervention to improve bariatric surgical outcomes. *Am J Physiol Regul Integr Comp Physiol* 311: R558–R563, 2016. First published July 27, 2016; doi:10.1152/ajpregu.00175.2016.—Thirteen percent of the world's population suffers from obesity and 39% from being overweight, which correlates with an increase in numerous secondary metabolic complications, such as Type 2 diabetes mellitus. Bariatric surgery is the most effective treatment for severe obesity and results in significant weight loss and the amelioration of obesity-related comorbidities through changes in enteroendocrine activity, caloric intake, and alterations in gut microbiota composition. The circadian system has recently been found to be a critical regulatory component in the control of metabolism and, thus, may potentially play an important role in inappropriate weight gain. Indeed, some behaviors and lifestyle factors associated with an increased risk of obesity are also risk factors for misalignment in the circadian clock system and for the metabolic syndrome. It is thus possible that alterations in peripheral circadian clocks in metabolically relevant tissues are a contributor to the current obesity epidemic. As such, it is plausible that postsurgical alterations in central circadian alignment, as well as peripheral gene expression in metabolic tissues may represent another mechanism for the beneficial effects of bariatric surgery. Bariatric surgery may represent an opportunity to identify changes in the circadian expression of clock genes that have been altered by environmental factors, allowing for a better understanding of the mechanism of action of surgery. These studies could also reveal an overlooked target for behavioral intervention to improve metabolic outcomes following bariatric surgery.

OBESITY IS DEFINED AS A BODY MASS INDEX of $\geq 30 \text{ kg/m}^2$ and promotes hypertension, dyslipidemia, insulin resistance, increased adiposity, obstructive sleep apnea, Type 2 diabetes mellitus, adverse cardiovascular function, polycystic ovary syndrome, asthma, back and lower extremity weight-bearing degenerative problems, development of several forms of cancer, and depression (3, 26). The World Health Organization (WHO) has described obesity as the greatest current threat to human health (41). As of 2014, the WHO global estimates of obesity and overweight conditions stated that more than 1.9 billion adults (18 years or older) were overweight, and that of this population, 600 million were obese (39). The causes of this epidemic are not fully understood and are likely to involve multiple, complex etiological interactions between endogenous factors (genetic, neuroendocrine, and metabolic) and exogenous factors (sleep/wake schedule, physical activity, dietary habits, and social influences) (26).

Mammalian species use the light-dark cycle as their primary source of circadian entrainment (5). As shown in Fig. 1, this cycle serves as a source of biological time keeping in that the suprachiasmatic nucleus (SCN), which contains the central pacemaker and generates a circadian rhythm that synchronizes peripheral clocks found in most metabolic tissues (5). Present in the SCN is a transcriptional-translational feedback loop of clock genes that is also operative in peripheral clocks (5, 19). Indeed, there are many behaviors, such as inappropriately timed and excessive intake of calorie-dense and nutrient-poor food items, sedentary behaviors, and ambient temperature control, which act to desynchronize peripheral clocks in metabolic tissues from the central clock that entrains to the environment. Interestingly, there is also strong evidence that increased exposure to light at night correlates with increased prevalence of obesity and metabolic disorders (8), suggesting that light-induced circadian misalignment is a prevalent modern condition. As such, it is likely that misalignment of the central and peripheral systems could contribute to obesity and the resulting adverse metabolic consequences.

Bariatric surgery is currently the most effective form of obesity intervention (1) and often consists of sleeve gastrec-

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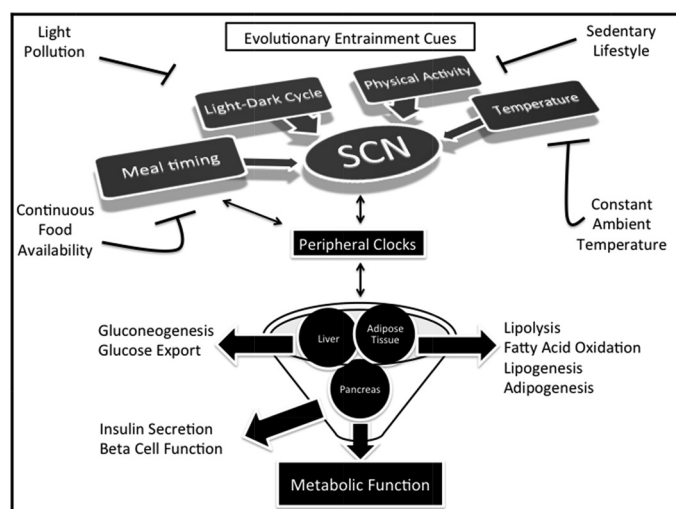


Fig. 1. Circadian disruptors negatively impact peripheral circadian clocks. Continuous access to calorie-dense foods, increasingly sedentary lifestyles, inadvertent light pollution, and living conditions under a constant ambient temperature all contribute to circadian disruption and the obesity epidemic. That these disruptors act to desynchronize the suprachiasmatic nucleus (SCN; central clock) from peripheral clocks, or directly affect the peripheral clocks, are novel risk factors as a result of modern society. Thus, circadian disruptors act on multiple metabolic tissues through external cues and promote the development of obesity and its associated comorbidities.

tomy (restrictive) with or without additional bypass of the gastrointestinal track (malabsorptive). Patients who undergo bariatric surgery show significant improvements in obesity-related comorbidities and weight loss (8). The health benefits seen in the postsurgical period are due to multiple mechanisms that contribute in a concerted fashion to metabolic improvements and include changes in gut-structure physiology, decreased caloric intake, and changes in endocrine hormone levels that are implicated in systemic metabolism and control feelings of hunger (29, 42).

Bariatric surgery, with its profound impact on both body weight and insulin resistance, provides an exceptional opportunity to study the link between obesity, circadian rhythms, and metabolism. An integrated network of clock genes present in both central and peripheral clocks underlies the generation and maintenance of circadian rhythms (16, 19). Many endocrine hormones exhibit a circadian pattern of release, suggesting the importance of a well-defined circadian rhythm in systemic metabolism (4), and their dysregulation may contribute to weight gain and the development of metabolic disorders. The fact that bariatric surgery provides robust improvements in insulin sensitivity and other hormonal profiles well before significant long-term weight loss is of particular interest and may be a function of changes in clock gene expression. The use of bariatric surgery to investigate the deleterious outcomes of circadian misalignment may reveal previously unknown mechanisms underlying the benefits of surgical weight loss procedures. Conversely, the employment of central circadian alignment in bariatric patients, such as fixed sleep/wake and meal times, could further augment the beneficial metabolic results obtained following surgery.

Balancing Good and Bad: How Modern Societal Advancements Have Led to Increased Desynchronization Between Central and Peripheral Clocks

Humans have benefited from modern advancements, such as the nearly ubiquitous availability of food at any given hour, and 24-hour access to light sources, enabling us to extend activities late into the night that have transformed society into an efficient, prosperous world. The problem with these advances is that the biology that once allowed us to survive in times of famine and food scarcity may now be working against our individual and collective health. Indeed, these “new” normal cultural practices may be detrimental to health both through external circadian misalignment, as well as internal circadian desynchrony.

Two Examples of Forced Desynchrony

Shift work. One by-product of shift work seems to be desynchronization of endogenous circadian rhythms (21). Shift workers live much of their lives desynchronized from the natural light-dark cycle since their sleep-wake cycles are chronically shifted or reversed (40). These individuals are often sleep restricted and engage in waking behaviors (e.g. work, eating) during the night at times when sleep should normally occur. Over 20% of the industrialized world engages in shift work, and this lifestyle is associated with Type 2 diabetes mellitus (T2DM), obesity, metabolic syndrome, and chronic sleep loss, making it a foundational example of the links between circadian disruption and metabolism (14, 21, 40).

Both the timing of consumption and quality of food also contribute to these metabolic outcomes given that peripheral clock function is strongly influenced by cellular nutrient sensors (31). Consequently, an additional risk factor, increased food availability, likely contributes to the obesity epidemic via peripheral circadian misalignment (24). Therefore, individuals who engage in shift work, consume meals at abnormal times, or who frequently consume calorie-dense foods may risk additional circadian misalignment and the development or worsening of metabolic symptoms.

Social jetlag. The impact of our social environment on sleep behavior can be demonstrated by the mismatch between the sleep duration on work/school days and on days free of waking obligations where sleep may persist longer than usual (15). Strikingly, 80% of the global population uses alarm clocks to force waking for some social obligation (37). This forced desynchrony has been coined “social jetlag,” a form of circadian misalignment due to a mismatch between endogenous circadian clocks and social obligations (36). Indeed, one of the most high-risk behaviors in modern society is shifting sleep-wake cycles to abnormal times (37).

The prevalence of this phenomenon raises concerns for individuals who are forced to work long or abnormal hours, as well as for those with obesity who generally have a later chronotype (36). It has been found that 69% of people in the industrial world experience at least one hour or social jetlag per week and 33% suffers from at least two hours (11). Strikingly, with every hour of social jetlag, the chances of excess weight gain increase by 33% (11, 37). This phenomenon also puts individuals at risk for adverse metabolic outcomes. Qin et al. (34) studied the 24-h endocrine profiles of medical students

under conditions of a diurnal or nocturnal lifestyle and found that nocturnal life leads to impaired glucose-stimulated insulin response.

Not only does insufficient sleep have adverse metabolic consequences, but Hanlon et al. (18) have demonstrated that sleep restriction activates the endocannabinoid system, a key component of hedonic pathways involved in modulating appetite and food intake. Therefore, a state of sleep deprivation due to later chronotypes or social obligations may also contribute to an increased risk of obesity through reward mechanisms, highlighting the importance of circadian alignment at multiple levels.

It is very likely that changes in the timing of food intake and the severity of circadian misalignment result in adverse systemic effects and obesity (44). These two examples of forced circadian desynchronization highlight the prevalence and severity of circadian misalignment in modern society and its profound ability to impair metabolism. In summary, circadian misalignment can induce systemic metabolic changes that increase the risk of weight gain and insulin resistance.

Illuminating Obesity: Light at Night as a Potent Source of Circadian Disruption

Humans have become increasingly exposed to artificial light in their nocturnal environments, forcing a gradual shift away from perceiving the naturally occurring light-dark cycles (8, 43). One of the most common forms of nighttime light exposure is light pollution, described as incidental exposure to light at night due to sky glow and street lighting (27). This is demonstrated by the fact that 99% of the European and American populations experience this phenomenon (9, 43).

Increasing prevalence of exposure to light at night has metabolic health consequences (9, 37). Many humans intentionally expose themselves to light at night by watching television, using computers and other electronic devices directly before bed, and turning on electric lights after sunset, which have been identified as risk factors for obesity, diabetes, and the metabolic syndrome (9, 10). Fonken et al. (10) have reported that exposure to ecologically relevant levels of dim light at night in mice attenuated circadian clock gene and protein rhythms, changed feeding behavior, and led to weight gain (10). Although the exposure of humans to "light at night" in the industrial world clearly precedes the onset of the current obesity epidemic beginning in the 1990s, the increased usage of personal electronic devices directly in bed may be a further aggravating factor.

Shift work, with intentional exposure to light, results in repeated and often long-term circadian disruption, subjecting them to a combined effect from sleep deprivation, mistimed consumption of food, and exposure to light at night (12, 15, 27, 31). Epidemiological evidence from shift workers suggests that prolonged exposure to light at night increases the risk of developing cancer, cardiovascular disease, and an elevated body mass index (BMI), as well as increased triglyceride levels and poor cholesterol balance (9, 40). Together, this suggests that light at night is a modern risk factor for obesity and metabolic disease since circadian clock function is clearly disrupted in several metabolically relevant peripheral tissues.

Bariatric Surgery: an Increasingly Prevalent Approach to Treating Morbid Obesity

Obesity can be broadly defined as an imbalance between energy intake and energy expenditure that leads to excessive fat accumulation in visceral and subcutaneous depots (26). Each year, roughly 2.8 million people with obesity or who are overweight die due to metabolic complications (29). Obesity has substantial associations with hypertension, coronary heart disease, dyslipidemia, T2DM, gastroesophageal reflux disease, nonalcoholic fatty liver disease, cancer, and obstructive sleep apnea (3). Bariatric surgery, with the most common procedures consisting of sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion with duodenal switch (BPD/DS), demonstrates the most effective form of treatment for morbid obesity and provides long-term weight loss and improvements in comorbidities (22).

Effectiveness of bariatric surgery on ameliorating obesity-related comorbidities. Bariatric surgery frequently leads to significant metabolic improvements. In a retrospective study of 168 severely obese patients who underwent RYGB, total cholesterol decreased by 12.5%, LDL decreased by 19%, triglycerides decreased by 41%, HDL increased by 23%, and the total number of patients afflicted by dyslipidemia decreased from 82% to 28% (33).

Type 2 diabetes mellitus remission in obese patients following bariatric surgery has also been widely reported. Rao et al. (35) found that RYGB, BPD/DS, and SG all produced early decreases in insulin resistance. They concluded that bariatric surgery is effective in resolving diabetes, although whether this was due to improved β -cell function (insulin secretion), increase in β -cell mass, decrease in insulin resistance, or some combination was not determined. Interestingly, these effects have been observed only days after surgery, if not immediately after, suggesting that remission of T2DM is mediated by a weight loss-independent mechanism (3). Indeed, Frikke-Schmidt et al. (11a) hypothesize that bariatric surgery can affect adipose tissue function in novel ways that are not fully explained by the traditional understanding of these procedures. For example, shifting fat distribution from visceral to subcutaneous depots resulted in enhanced insulin- and catecholamine-mediated sensitivity of lipolysis and decreased adipose inflammation. Therefore, not only does bariatric surgery promote sustained weight loss, but it is also effective in managing a wide range of comorbidities and systemic metabolic function (42). However, the connections between bariatric surgery, the resetting of the peripheral clocks, and improved metabolic outcomes in humans remain poorly understood.

Caloric restriction, an immediate effect of all surgical interventions, likely plays an important role in the favorable metabolic changes observed after bariatric surgery (28). However, the mechanical effects of procedures like RYGB on the gastrointestinal tract, such as reduced nutrient absorption and gastric pouch size, cannot fully account for the extent and magnitude of metabolic improvements. It has been widely accepted that the complex changes in the gut that affect multiple organs through metabolic signaling and endocrine mechanisms can link RYGB to decreased cardiovascular risk and changes in lipid absorption and bile acid metabolism (23). Altered vagal nerve function associated with hypothalamic

centers responsible for hunger, appetite, and satiety (28) may also play a role.

It has been proposed that sustained weight loss may be a function of restored adipokine concentrations and changes in adipocyte protein expression, both of which are under circadian control (16). Enhanced peripheral insulin sensitivity may be mediated through an increase in secretion of adiponectin from fat cells. Adiponectin is inversely proportional to body fat mass, BMI, waist-to-hip ratio, serum insulin, and glucose levels; low levels are closely correlated with insulin resistance, while increased levels have been associated with enhanced insulin sensitivity (28). Most studies have reported an increase in adiponectin levels after RYGB, which correlates with the improvement in insulin resistance following surgery (29, 35). Although the true mechanism has yet to be confirmed, it is possible that the restoration of adipokines following bariatric surgery is mediated through restoring normal circadian expression.

Widespread changes in behavioral aspects of patients who undergo bariatric surgery. Bariatric surgery has also been shown to induce a variety of behavioral changes in patients who undergo the surgery that may contribute to the effectiveness of the procedures. Interestingly, behaviors that are corrected by bariatric surgery are those that serve as circadian disruptors that can lead to obesity, such as calorie-dense food preference, altered sleep duration and quality, and sedentary lifestyles.

As previously noted, sleep quality and duration are intimately tied to metabolism and highly vulnerable to circadian disruption due to environmental cues such as light at night. Obesity is closely correlated with an increased prevalence of obstructive sleep apnea, and the associated sleep fragmentation and intermittent hypoxia cause additional adverse metabolic effects (32). It is also well documented that bariatric surgery reduces respiratory disturbances during sleep and that, in general, obesity-related sleep disorders improve markedly in patients who undergo bariatric surgery (6).

Improper meal timing and calorie-dense food preferences are two behavioral aspects associated with obesity and have direct impacts on peripheral circadian functions (12, 31). Multiple studies highlight the effectiveness of bariatric surgery in leading to substantial changes in neural responses to food cues, which subsequently lead to selective reductions in preference for calorie-dense foods (30). Postoperative patients have decreased cravings for calorie-dense foods, exhibit decreased preference for sugary foods, are less hungry, and prefer healthier food options (25). Taken together, these studies suggest that bariatric surgery is capable of resolving various behavioral activities that are implicated in circadian disruption and the development of obesity.

Bariatric Surgery: A Possible Mediator of Metabolic Improvements Through Resetting the Phase and Amplitude of Peripheral Circadian Clocks

Despite the previously reported links between circadian behavior and systemic metabolism, the molecular links between individual chronotype, peripheral circadian gene expression, and adipocyte insulin sensitivity remain poorly understood. It is possible that reduced insulin sensitivity of adipose tissue in individuals with obesity is, in fact, partially mediated

by alterations in the expression of circadian rhythm-controlled metabolic genes. Bariatric surgery may not only aid in restoring metabolic integrity through mechanical manipulations of the gastrointestinal tract, but through a rapid resetting of the peripheral clocks in adipose tissue.

The three current methods of obesity intervention—behavioral, pharmacological, and bariatric surgery—would be ideal places to begin investigating the possibilities of intervening in obesity through resetting the circadian clock. In fact, Zhang et al. (45) quantified a peripheral clock gene, *Rev-erba*, in adipose tissue of nonobese diabetic Goto-Kakizaki rats with congenital β -cell defects and insulin resistance. They reported that after bariatric surgery, expression of this gene was indistinguishable from control rats and that their metabolic symptoms had also been ameliorated. This study suggests that altering clock gene expression through bariatric surgery is likely a contributing mechanism to the improved metabolic profiles observed in transgenic animal models with disrupted peripheral circadian clock function, a finding that may be particularly relevant to obese human patients.

Conclusions

Obesity has become a serious global health concern, as populations worldwide are becoming increasingly overweight. Although bariatric surgery is now frequently employed to treat obesity and its related comorbidities in its most severe forms, in actuality, fewer than 1% of individuals who are potential candidates actually undergo surgery (7). Bariatric procedures were once thought to induce metabolic improvements solely through mechanistic manipulations to the gastrointestinal tract; however, it is now known that there exist contributions by altered hormones and protein expression in metabolic tissues (3). The possible mechanisms behind weight loss and amelioration of obesity-related comorbidities is now the subject of current research—including this review—and will be imperative to understand in order to optimize these effects and to discover novel treatment methods.

In recent years, an emerging understanding of the links between sleep, circadian regulation, and metabolism has led to the recognition that disturbance of the circadian clock system is a putative novel risk factor for weight gain and insulin resistance. It is now well known that central entrainment to the light-dark cycle is crucial for a healthy lifestyle and metabolic function (15). With advances in molecular biology and widespread epidemiological studies, it has been demonstrated that when an individual is not centrally aligned to their environment, circadian expression of clock genes is altered, which can lead to metabolic syndrome and obesity. Conversely, sleep extension in humans improves fasting insulin sensitivity, as well as reduces the diabetes risk induced by acute sleep deprivation (2, 20). The development of novel behavioral and pharmaceutical interventions aimed at improving sleep quality/duration and resetting peripheral clock entrainment could provide novel therapeutic options for intervention in obesity and insulin resistance.

Indeed, the possible interaction between circadian rhythms and bariatric surgery in the improvement of metabolic health needs further investigation. Clearly, dysregulation of circadian timing in a variety of real-world settings is associated with increased risk for weight gain and metabolic comorbidities.

What remains to be determined is 1) whether bariatric surgery can reset the central and peripheral circadian rhythms, and 2) whether central circadian intervention (set times for meals, lights off/on for bed times) can enhance the postoperative improvements in weight loss and systemic insulin sensitivity in human patients. Given our knowledge of the risk factors and causes of central circadian misalignment, postoperative guidance from bariatric surgeons emphasizing the importance of both meal and sleep timing in circadian realignment may improve the success of surgical outcomes.

Future Directions

Using bariatric surgery in translational research to explore the role of peripheral circadian clocks for obesity intervention. Bariatric surgery provides an exceptional opportunity to examine pathways linking the circadian system, adipocyte function, and systemic metabolism. It has been shown that a robust improvement in insulin signaling in adipocytes is evident as early as days after surgery, well before significant weight loss has occurred (35). No study to date has reported the impact of bariatric surgery on circadian gene expression patterns or insulin signal transduction in human peripheral tissues, including adipose tissue.

Given that bariatric surgery induces beneficial metabolic changes and that circadian disruption opposes this, a study examining the expression of peripheral clock genes before and after bariatric surgery may reveal previously unknown mechanisms underlying obesity and improvements following these procedures. The possibility of identifying clock genes whose expression is modified by bariatric surgery would provide novel information as to where and how intervention should be targeted. Not only would this allow specific pharmacological intervention, but also this would provide an opportunity for bariatric surgeons to become more informed to potentially improve postoperative patient outcomes through patient instruction.

Eating behavior, as well as sleep duration and quality, are partly predicted by chronotype. Individuals with later chronotypes eat a higher proportion of daily caloric intake in the evening and are at higher risk for weight gain and shorter sleep duration than early chronotypes (14, 31). Conversely, a study of 420 individuals in a 20-wk weight loss regime revealed that late eaters lost less weight and displayed a slower weight loss rate than early eaters, despite similar energy intake, dietary composition, estimated energy expenditure, appetite hormones, and sleep duration (13). With this knowledge, specific instructions advising patients when to consume food to avoid eating at circadian desynchronized times, as well as what types of food they should eat, can be provided to improve surgical outcomes.

Furthermore, knowledge of behavioral intervention with respect to sleep alignment may be another lifestyle change that can be advocated for by bariatric programs. Nearly two decades of complex and extensive clinical research on sleep, circadian rhythms, and glucose metabolism has been conducted, and the impact of the behavioral alignment of the central clock on peripheral clock function and insulin sensitivity in adipose tissue is well documented (21). A recent study has demonstrated that an earlier timing of food intake was correlated with enhanced weight loss following bariatric surgery, while poorer weight loss responders exhibited average

later daily times of food consumption (38). Properly aligning and scheduling exposure to dark and fixed bedtimes may ameliorate the results that several experimental studies have demonstrated on the deleterious metabolic effects of circadian misalignment in humans. The possibility that this behavioral alteration might represent an intervention with metabolic benefits has never been tested and would offer a novel treatment option for bariatric surgeons. Bariatric surgery is currently an effective means of intervention, but it should also be used as a gateway to further understand the obesity epidemic such that bariatric surgeons can provide optimal clinical outcomes to their patients.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health Grant R01-DK-103014 (to M. J. Brady).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

K.N.K. drafted manuscript; K.N.K., E.C.H., V.N.P., and M.J.B. edited and revised manuscript; K.N.K., E.C.H., V.N.P., and M.J.B. approved final version of manuscript.

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