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REVIEW ARTICLE

Obesity and metabolic syndrome: Association with chronodisruption, sleep deprivation, and melatonin suppression

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Abstract

Obesity has become an epidemic in industrialized and developing countries. In 30 years, unless serious changes are made, a majority of adults and many children will be classified as overweight or obese. Whereas fatness alone endangers physiological performance of even simple tasks, the associated co-morbidity of obesity including metabolic syndrome in all its manifestations is a far more critical problem. If the current trend continues as predicted, health care systems may be incapable of handling the myriad of obesity-related diseases. The financial costs, including those due to medical procedures, absenteeism from work, and reduced economic productivity, will jeopardize the financial well-being of industries. The current review summarizes the potential contributions of three processes that may be contributing to humans becoming progressively more overweight: circadian or chronodisruption, sleep deficiency, and melatonin suppression. Based on the information provided in this survey, life-style factors (independent of the availability of abundant calorie-rich foods) may aggravate weight gain. Both epidemiological and experimental data support associations between disrupted physiological rhythms, a reduction in adequate sleep, and light-at-night-induced suppression of an essential endogenously produced molecule, melatonin. The implication is that if these problems were corrected with life-style changes, body-weight could possibly be more easily controlled.

Key words: Brown adipose tissue, circadian rhythms, light: dark cycle, melatonin, metabolic syndrome, obesity, sleep

Introduction

In the mid-twentieth century, an obese individual was the exception; by the mid-twenty-first century it may be the norm. As grave as this estimate may sound, in some countries, e.g. the US and other advanced and/or wealthy nations, the new norm may, in fact, be reached well in advance of the year 2050. At the current rate of weight accumulation by humans, Wang and colleagues (1) have predicted that, as soon as 2030, 85% of the US adult population will qualify as being overweight and 50% will exceed the obesity criterion. To classify an adult human as obese requires a body mass index (BMI)>30 kg/m² for class 1 obesity, a BMI of 35–39.9 kg/m² as class 2 obesity, and a BMI of >40 kg/m² as being class 3 obese (grossly or morbidly obese) (2).

Kelly et al. (3) rendered essentially the same prediction as Wang et al. (1); thus, the abundance of calorie-rich food and the indifference to exercise will make obesity the likely scenario for a majority of the adult population within the next two decades.

Making matters worse, obesity is no longer an affliction limited to adults but it now afflicts the adolescent and younger populations as well (4,5). Indeed, childhood obesity has become rampant, and, as a consequence, children are acquiring diseases and disorders that were typically only common in adults a couple decades ago. Moreover, humans have inflicted the obesity state on their pets as a result of over-feeding and by limiting their activity.

Historically, there were two virtually unavoidable options for limiting fat accumulation. Thus, humans

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Key messages

- Chronodisruption, i.e. disturbances in the circadian system, may contribute to obesity or its co-morbidities.
- The gradual reduction in sleep duration that has occurred in humans over the last five decades is associated with an increased frequency of obesity.
- In animals, melatonin supplementation reduces body weight and obesity without altering food intake.

ate less, which during previous centuries was much easier to achieve given the frequent scarcity of readily available food, and they, by necessity, exercised more. Again, this latter feature was inescapable since a large amount of energy was often expended securing the next meal and, in the absence of modern conveniences, food preparation required significantly more effort. Rather than having to find, chase, harvest, and prepare food, in current societies readily edible food essentially comes to us.

The relatively small amount of body fat that our predecessors did have was important in past epochs when food availability was unreliable. It was essential to hoard calories in the form of adipose tissue when the timing of the next meal was precarious. If not required for the immediate energy needs, the excess fuel was transformed into triglycerides which were deposited in fat cells. This stored energy was then dispatched when the metabolic requirements of the body exceeded those provided by recently consumed food or when limited food was available. In many modern societies, food is so easily available that any stored energy is not used, rather more is deposited.

Such massive stores of energy as fat are detrimental as evidenced by the fact that overweight humans have a higher incidence of a variety of serious co-morbid disorders including cardiovascular disease, diabetes and metabolic syndrome, cancer, orthopedic problems, etc. (6-8). This has placed, and will continue to place, great burdens on medical services to provide adequate treatment and care for the increasingly larger number of individuals who are currently, or will be, overweight. Unfortunately, considering the current and expected trends, the problems of obesity and associated disease risks will become more frequent before they improve. Indeed, improvement will only be possible when there is a clearer understanding of the mechanisms of obesity and we are committed to do something about it.

In this review, we consider the potential role that the circadian system including the sleep/wake cycle

Abbreviations

| BAT | brown adipose tissue |
|-----|--------------------------|
| BMI | body mass index |
| CD | chronodisruption |
| HDL | high-density lipoprotein |
| LDL | low-density lipoprotein |
| SCN | suprachiasmatic nuclei |
| | |

and the melatonin rhythm may play in determining the accumulation of fat. Given that the daily endogenous melatonin cycle with low circulating levels during the day and elevated serum levels at night, along with the fact that light at night suppresses or distorts this regularly recurring rhythm, we proposed that excessive night-time light may contribute to physiological alterations that predispose to obesity (9,10). Moreover, circadian disruption and especially shortened daily sleep intervals, independent of the changes in the melatonin cycle, have been suggested to be contributory to metabolic diseases, which accompany obesity (11-13). The implication is that circadian disruption or chronodisruption (14) and the resulting sleep deprivation and relative melatonin deficiency, alone or in combination, may be factors that make humans more likely to gain weight. If this is the case, there may be behavioral adjustments that humans could make to redress, at least partially, the continuing and mounting problem of obesity.

The circadian system, sleep, and the melatonin rhythm

Animals, including humans, evolved over millions of years in a stable, albeit seasonally changing, light:dark environment where the intervals of light and darkness were distinctly separated during each 24-hour period. As a consequence of this highly regular and repeating cycle, vertebrates developed an internal neural clock to take advantage of the light:dark cycle and to adjust their physiology accordingly. This became the basis of circadian rhythms. The vertebrate biological clock is located in neurons in the suprachiasmatic nuclei (SCN) of the anterobasal hypothalamus. The SCN is the chronometer that determines the regular fluctuation of virtually every function in the organism; it is the central generator of circadian rhythms (15,16). The seasonally changing light:dark cycle, via the SCN, functions as both a clock and a calendar in vertebrates and is a major determinant of daily and seasonal fluctuations in physiology (17).

One obvious cycle that clearly depends on the prevailing light:dark cycle and the function of the SCN is the melatonin rhythm. All vertebrate species, regardless of their specific circadian activity pattern, experience elevated pineal melatonin production and secretion during the night, with minimal synthesis during the day. As a result, melatonin is often referred to as the 'chemical expression of darkness' (18). Since pineal melatonin is quickly released once it is produced, the melatonin rhythm in the blood reflects its synthesis within the pineal gland.

The melatonin cycle has a number of essential physiological actions. One important function is to apprise cells in the organism as to whether it is day or night, with the cells then using this information to adjust their metabolic activity accordingly (17). Thus, although the SCN has alternative means in addition to the melatonin cycle for signaling light or darkness at the cellular/organ level, there is little doubt that the fluctuating melatonin levels play an important role in conveying essential timing information to many organs.

The regularly recurring melatonin cycle assists animals, including humans, to adapt to and remain in synchrony with their external environment. A conspicuous example of this is the seasonal reproductive rhythm in photoperiodic mammals, which is destroyed when animals are pinealectomized or when their melatonin rhythm is altered (19). In humans, the melatonin cycle is essential for circadian timing; for example, it impels the normal sleep/wake cycle which is important for optimal health.

Unfortunately, humans have undermined the function of the SCN and have subverted the melatonin cycle and the sleep/wake rhythm by contaminating the normal period of darkness with the wide-spread use of artificial light, which distorts circadian rhythms and results in suppression of elevated night-time melatonin levels (20,21). This has become especially apparent within the last six decades, and, moreover, it is getting progressively worse. Thus, when photographs taken at night from outer space are viewed, it is obvious that night/darkness is disappearing, particularly in areas of high population density. While the common use of manufactured light has provided many benefits, e.g. greatly increased productivity, it has likewise created physiological problems as well, e.g. increased fatigue and work inefficiency by individuals working the night-shift. In more extreme cases, pathophysiological changes may occur, e.g. increased cancer risk (22-25). The availability of light at night also shortens the daily duration of sleep by allowing humans to remain active well after sunset or before sunrise.

In addition to disturbing the melatonin rhythm, physiological disorders that accompany night-time light exposure may also be a consequence of generalized circadian disruption or what is referred to as chronodisruption (13). Thus, in addition to obviously altering the 24-hour melatonin cycle, light at night provides the SCN inappropriate information about the time of day, which is subsequently communicated to other organs. The cells of all peripheral organs are endowed with a set of circadian genes, the activity of which depends on the proper information provided by the SCN, to allow these cells to function optimally (16,26). When they receive improper information from the master circadian generator, the function of the cells suffers and, especially if the disturbances are prolonged, pathologies likely develop.

One easily measurable rhythm that is obviously disordered by alterations of the circadian clock is the sleep/wake cycle. This is readily seen in the phenomenon of 'jet lag' (27). Performing rapid transmeridian travel across multiple time zones, particularly in an easterly direction, requires the SCN to readjust its signal to the new light:dark environment after arrival. During this period of readjustment, individuals experience sleep disturbance, increased fatigue and general malaise, i.e. 'jet lag', with conspicuous disturbances in the 24-hour melatonin cycle (28).

It is not necessary, however, to travel across multiple time zones to become sleep-disturbed and fatigued and to distort the circadian network. Individuals living in modern societies make activity adjustments that also cause similar chronodisruptions. For example, shift workers, who account for an estimated one-fourth of the work-force worldwide, experience such disturbances on a regular basis (29). Also, individuals who for other reasons (e.g. social) maintain an irregular and/or inconsistently shifted light/dark or sleep/wake cycle have a similar problem with disturbed circadian rhythms. Similarly, people who regularly interrupt their period of darkness with even brief intervals of light repeatedly provide the biological clock with incorrect information which is passed downstream to cells at the peripheral level. This may be also manifested in children by their propensity to remain active well into the night and/or the fact that they may sleep with the lights on at night, something that should be absolutely discouraged.

For the purposes of the current survey, the issue is, how serious is the impact of circadian disturbances on weight gain and its co-morbid disorders? If there are, in fact, health consequences of circadian perturbations, melatonin suppression, and sleep deficiency, it is essential that they be identified so corrective actions can be taken.

Circadian disruption (chronodisruption) and obesity

Adipose tissue is not as inert as once thought. Adipocytes are highly metabolically active and synthesize

and secrete a number of proteins, e.g. adiponectin, resistin, visfatin, etc., which influence food intake and metabolic activity (30). Moreover, there are multiple hormones from the gut, e.g. ghrelin, etc., which influence appetite, food consumption, fat deposition, and metabolism (31). Disturbances in the production or release of these factors could well influence the timing of food intake and the quantity of fat that is deposited in the body. This is an aspect of obesity which is under investigation and deserves more attention.

As with genes in other cells, some of those in adipocytes exhibit circadian rhythms (32). It is estimated that 7%–21% of the genes in both white and brown adipose tissue fluctuate with a periodicity of 24 hours (33). Additionally, these circadian changing genes trigger the activity of other genes in fat cells, i.e. the clock control genes (34). Considering these complex interactions, it is obvious that distortions in the physiology of the central rhythm generator, i.e. the SCN, have a major impact on the function of the adipocytic genetic machinery.

Chronodisruption (CD), including both central and peripheral desynchronization of circadian physiology, induces adverse health outcomes (14). CD causes internal circadian disorder in the most basic aspects of cell function, thereby predictably leading to the development of pathophysiology. The resulting disordered physiology and/or pathology has most frequently been evaluated, in humans, in night-shift workers (23,24) and in those repeatedly suffering from transitory 'jet lag' (35). In human adipose tissue, for example, the rhythms of many genes are pronounced (>30%). Moreover, when examining gene expression in adipose tissue, and especially subcutaneous adipose tissue, the data showed that the circadian rhythmicity followed predictable physiological patterns (36). Additionally for each gene, protein mRNA levels fluctuated during the day in synchrony with its receptor.

A major problem with the activities of modern humans is that we are living a twenty-first century life-style with an ancient genome, which is not compatible with the artificially altered photoperiods. Thus, humans have corrupted the fundamental circadian physiology by polluting night-time darkness with light. This extraordinary perturbation of the regularly recurring light:dark environment, a cycle which has existed throughout human evolution, has negative consequences on the most critical functions of the SCN and all peripheral oscillators. Over millions of years of evolution, humans (indeed, all animals) became physiologically dependent on the stable changes in day and night and, in fact, vertebrates evolved a clock, the SCN, to use the light:dark cycle to their advantage. With the advent of the discovery of artificial light in 1879, however, a major disturbance in the light:dark cycle occurred upsetting the function of the clock since its ancient genetic machinery could not rapidly accommodate to this tumultuous change.

It is not surprising that these drastic changes in the environment would lead to metabolic disturbances. Karlsson and co-workers (37) conducted a large epidemiological study of the association of shift work with metabolic disorders and found these individuals typically had an increased incidence of general obesity, abdominal obesity, hyperglyceridemia, depressed high-density lipoprotein (HDL), diabetes, and cardiovascular abnormalities. This populationbased study included 27,485 individuals. The findings clearly showed that the excessive weight gain is not the only disorder that accompanies chronic shift work, but also the expected co-morbidities that are a consequence of obesity were present.

A specific eating disorder that is related to CD is night-eating syndrome (38). Individuals afflicted with this condition are commonly obese, eat very little in the morning, but gorge themselves in the evening and usually suffer with insomnia. Endocrinologically, they have elevated blood cortisol concentrations and a reduced rise in night-time melatonin and leptin levels.

Genetic studies of obesity in humans have yielded some data linking CD to excessive food consumption and elevated body mass (39,40). It is also not uncommon, however, that CD individuals are short sleepers (41–43). Therefore, whether the resulting obesity is only a consequence of disturbances in circadian rhythmicity or whether it also involves altered sleep patterns (41–43) or melatonin suppression (39) remains unresolved (see below).

As already alluded to, a major consequence of central/visceral obesity is metabolic syndrome, also known as insulin resistance syndrome, syndrome X, etc. While the requirements for the diagnosis of this syndrome vary somewhat, its major features typically include, in addition to central obesity, elevated blood pressure, dyslipidemia, low HDL cholesterol, elevated fasting plasma glucose, and microalbuminuria (44,45). While this syndrome is most commonly present in individuals with a large waist circumference and obvious obesity, patients who have a normal body weight may also have this syndrome. Besides being overweight, other major risk factors for this disease include prolonged stress, physical inactivity, type 2 diabetes, advancing age, and some other less frequently considered disturbances.

Within the last decade, the dependence of metabolism on the circadian system has been intensely investigated (15,46). A variety of hormones known to be involved in the control of metabolism—e.g. cortisol, insulin, glucagon, and growth hormone fluctuate in a circadian manner. Circadian mechanisms of cells also regulate some metabolic enzymes such as those related to cholesterol metabolism (46–48). Moreover, nuclear receptors related to the metabolism of glucose and lipids exhibit circadian rhythms (49).

In a cleverly designed series of experiments, Fonken and colleagues (50) recently showed that the exposure of Swiss Webster mice to light at night, which disrupted the timing of food intake but not the total amount of food eaten, caused the animals to gain weight beyond that measured in control mice maintained under a regular light:dark cycle. The night-time light that was used in this study surely reduced the high levels of melatonin that would have occurred during the normal period of darkness, although melatonin was not measured. The experimental design used, therefore, would certainly have caused a melatonin deficiency (like pinealectomy) and, opposite to melatonin administration, the altered light:dark environment elevated body weight and adiposity.

The authors of the report concluded that the timing of food intake (rather than the total amount of food consumed, which was not influenced), due to CD, was critical in mediating the observed increased weight gain. It was speculated that nocturnal illumination led to metabolic abnormalities resulting from circadian rhythm misalignment. Fonken et al. (50) cited other papers which also showed that metabolic circadian rhythm perturbations including that of the 24-hour melatonin cycle are intrinsically related (51–53). The specific metabolic alterations that in fact occur under conditions of CD have not, however, been well defined.

As already mentioned, animal and human adipocytes possess circadian oscillators suggesting they may influence the development of metabolic syndrome. Molecules specific to fat cells that exhibit circadian rhythmicity include leptin, visfatin, adipsin, resistin, and adiponectin (54,55).

Blood pressure normally exhibits a circadian rhythm with lowest systolic and diastolic pressures at night (56). When this circadian pattern of blood pressure, as well as endothelial and hemostatic function, is absent, the likelihood of insulin resistance and the associated tissue damage is exaggerated (57). A recent publication reported that a disturbance in the circadian blood pressure rhythm also occurs in obese children (58).

Clock gene expression has been compared in visceral and subcutaneous fat obtained from morbidly obese men with correlations being made with metabolic syndrome in these individuals (59). In both visceral and subcutaneous fat deposits, Bmall expression was lower than that of Per2 and Cry1. In subcutaneous fat cells, the expressions of clock genes were highly correlated with each other, a feature that did not occur in visceral fat. The authors reported that Per2 gene expression in visceral fat was inversely correlated with waist circumference, while each of the genes investigated was significantly and negatively correlated with low-density lipoprotein (LDL) and total cholesterol levels (59).

While there are some obvious associations between perturbations of circadian hormone rhythms, disturbances of circadian rhythms in adipocytes, 24-hour blood pressure alterations and correlations between clock gene expression and some aspects of metabolic syndrome, a clear definition of how these disturbances relate to the development of metabolic syndrome has not been forthcoming. At the current state of the science, it seems obvious that some of the parameters investigated are correlated with the symptoms of metabolic syndrome; however, whether they are a cause or an effect of the syndrome remains for future studies to determine.

One of the most complete investigations on the relationship of fatness, fitness, and life-style to metabolic syndrome is that of Ferreira and colleagues (60). This group investigated the time course of potential determinants of metabolic syndrome in individuals from 13 to 36 years of age; the study included 364 individuals of whom 189 were females. The potential determinants of interest were body fatness and fat distribution, cardiopulmonary fitness, and life-style. At 36 years of age, 10.4% of the subjects were diagnosed with metabolic syndrome. These individuals (relative to those without the syndrome) had 1) a marked elevation of body fat and visceral fat, 2) a reduction in cardiopulmonary fitness, 3) a lower frequency of intense physical activity although a slightly greater frequency of light and moderate activity, 4) reduced alcohol intake, and 5) a tendency to higher energy intake. The authors concluded that multiple processes and mechanisms contribute to the development of metabolic syndrome and, importantly, the pathogenesis of the syndrome begins early in life (60). Hence, strategies to combat the disease must be initiated early in life and must be multifactorial.

That molecular perturbations of the neural biological clock, i.e. the SCN, may be directly involved with obesity and metabolic syndrome is suggested by the work of Turek and colleagues (11). The CLOCK transcription factor is a major component of the pacemaker neurons in the SCN. Turek et al. (11) reported that homogenous CLOCK mutant mice exhibit a variety of changes consistent with metabolic syndrome, including alterations of diurnal feeding rhythm, hyperphagia, obesity, hyperleptinemia, hyperlipidemia, hepatic steatosis, hyperglycemia, and hyperinsulinemia. These findings in mice certainly provide suggestive evidence that, in humans as well, disturbances in the molecular mechanisms in the SCN could be related to the manifestation of metabolic syndrome.

The results of the Turek et al. (11) study have been confirmed and extended in a more recent noteworthy investigation. Thus, Karatsoreos and coworkers (61), rather than using a mutant mouse strain, reported that, in wild-type mice as well, CD due to perturbations of the photoperiod altered the metabolic characteristics of the animals consistent with those measured by Turek et al. (11). These observations in wild-type mice document that the physiological changes observed were environmentally driven and were not confounded by the unique genetic construct of the mutant mouse model.

Interestingly, the exposure to what are classified as unusual or abnormal photoperiods does not have to be chronic to induce potential health consequences. Sheer et al. (62) reported that even shortterm misalignment of circadian rhythms, similar to some of the scenarios suggested in the present review, caused quite significant metabolic changes in normal healthy adults. The conclusion of these collective studies is that both chronic, but even acute CD, especially if intermittently repeated, could translate into changes reminiscent of those seen in individuals suffering with metabolic syndrome.

Sleep deficiency and obesity

There is a strong correlation between the increasing prevalence of obesity and shorter sleep times, and available evidence indicates that a sleep deficiency may, in fact, contribute to excessive weight gain in both children and adults (13). Although most prominent in the US, this trend has become apparent in many industrialized countries. The progressive erosion of sleep time becomes apparent when one examines sleep history in the US over the last five decades.

In 1960, a survey taken by the American Cancer Society concluded that the usual sleep duration was commonly between 8 and 8.9 hours nightly (63). Using similar subjective measures of sleep, a poll by the National Sleep Foundation in 1995 reported that the average nightly sleep time had fallen to 7 hours (64). By 2005, an estimated one-third of adult men and women in the US claimed only 6 hours of selfreported sleep each night (65). With the aid of more objective estimates of sleep, the data seem to confirm a reduction in sleep time in both adults and children in the US in recent decades. Using measurements from actigraphs worn by 40–60-year-old adults at night and published in 2000, sleep duration averaged 6.2 hours (66). Home polysomnographic results of 2,685 individuals indicated a mean sleep duration of 6.1 hours for women and 5.7 hours for men (67). Roughly the same sleep durations were reported in the CARDIA sleep study published in 2006 (68). Similar short duration sleep times are common for children (13). Thus, on average, in the US, based initially on subjective sleep evaluation and more recently on objective measures, sleep duration in US adults and children has fallen by roughly 30% relative to that measured in 1960. Although there are fewer studies to support this conclusion, it is assumed similar trends in sleep duration reduction have occurred in other industrialized countries as well.

As mentioned above, this same time interval (1960 to present day) has been associated with an objective rise in body fatness and obesity. It is surmised that shorter sleep times affect energy balance by at least three means, i.e. appetite up-regulation, increased time and/or frequency of eating, and a reduction in energy expenditure (13). Excessive body mass often results in insulin resistance which promotes further adiposity. It is also commonplace that 20% of individuals who are overweight exhibit sleep-disordered breathing, e.g. sleep apnea, etc., which is an independent risk factor for insulin resistance further contributing to rises in body mass; this occurs in both children and adults (69,70). The published data are also convincing that sleep fragmentation, reduced levels of non-rapid eye movement sleep, and transient hypoxia, which often accompany disordered sleep, may act independently or combine to lower insulin sensitivity (71).

Early studies using rodents showed that neartotal sleep deprivation, a condition with only an extremely rare human correlate, was shown to increase food intake by animals (72). More recently, such investigations have been refined for the purpose of examining food intake and appetite in a situation approximating that which some humans experience, i.e. partial chronic sleep deprivation. Again, short sleep duration correlated with elevated food intake.

The laboratory of Van Cauter and colleagues (73) examined hormonal and metabolic variables in young men subject to recurrent partial sleep deprivation in what the authors refer to as the Sleep Debt Study (6 days with 4 hours bed (sleep?) time). This well controlled study in which all individuals had identical calorie intake, showed that the levels of leptin, the satiety factor, are significantly lower and hunger is elevated in sleep-restricted men. Thus, sleep loss lowered the feeling of satiety which would promote additional food intake. Extended over time, this imbalance would be expected to cause increased food consumption and weight gain. Although the magnitude of the changes in leptin levels were a little less pronounced, essentially similar data were reported by Chin-Chance et al. (74). In addition to the unexpected leptin response, the state of sleep debt reduces insulin sensitivity, which might elevate the likelihood of increased appetite, food intake, and weight gain (13).

In another laboratory-based study, ghrelin, a hormone that induces hunger, also responded to sleep deprivation in an unexpected way, i.e. it increased in the blood (75). This caused a major imbalance of the ghrelin-to-leptin ratio which was significantly correlated with and elevated hunger rating. Thus, reduced leptin (which promotes satiety) and a rise in ghrelin (which promotes hunger) would encourage greater food consumption. Of additional interest is that sleep deprivation stimulated the desire for carbohydrate-rich nutrients suggesting, as the authors note, that the sleep-deprived brain craves glucose, its primary fuel (75).

Population-based studies have yielded results remarkably similar to those obtained from investigations that examined sleep-deprived individuals in the laboratory setting. Both the Wisconsin Sleep Cohort Study (76) and the Quebec en Forme (77) investigation measured changes in either leptin and/or ghrelin in sleep-restricted individuals and reported changes consistent with the up-regulation of appetite, as was reported by Spiegel et al. (73,75) in the laboratory. Somewhat in contrast, in younger humans the responses to reduced sleep duration seem to exhibit gender differences. This study included children and adolescents 6-20 years of age (78). In boys with short sleep periods, energy expenditure was decreased, while girls' short sleep intervals were associated with elevated blood leptin levels. These differences may predict a greater frequency of obesity in young males over young females, a situation generally not supported by the percentage of boys and girls who are overweight.

Many, but not all, epidemiological reports have also contributed compelling evidence supporting the association between short nightly sleep and an elevated BMI (79-85). These studies involved thousands of individuals of both genders and included both children and adults. A systematic analysis by Patel and Hu (83) of many of these studies suggested that short sleep times have a greater likelihood of causing obesity in children than in adults and in voung adults versus those who are middle-aged. The outcomes of both cross-sectional and prospective studies support the association. While the results of some studies indicated no relation, on balance, there seems to be general agreement that duration of sleep does impact the BMI via changes in appetite and food intake. The findings are certainly consistent with observations of natural populations in industrialized countries where overweight is becoming the norm and 8-hour nightly sleep duration is becoming less common.

As with circadian rhythm disorders, sleep deprivation in addition to leading to increased obesity is accompanied by an elevated likelihood of developing diabetes and metabolic syndrome (13,84,85). Obesity and diabetes so often occur together in individuals with sleep deficits that the term 'diabesity' has been used to describe this combination of conditions.

Melatonin suppression and obesity

Melatonin, an endogenously produced molecule, is synthesized and secreted on a nightly basis by the pineal gland (86). Within the last decade, it has been found to have anti-obesity effects (10). Unlike studies related to sleep and obesity, which have been primarily based on observations in humans, to date studies linking melatonin to its ability to inhibit body weight have been exclusively performed in rodents.

Because of its secretion from the pineal gland at night, blood and cerebrospinal fluid levels are much higher at night than during the day (87,88). In humans, as in other animals, the duration of elevated melatonin is proportional to the length of the daily period of darkness (89). Most humans, of course, live in a highly artificial light:dark environment (i.e. relative to the normal light:dark cycle provided by the rising and setting of the sun) and are routinely exposed to bright light during their waking hours. Since light exposure, when of sufficient irradiance and proper wavelengths, prevents pineal melatonin synthesis (90,91), during a major portion of each 24-hour period humans have greatly attenuated, circulating melatonin concentrations. This contrasts sharply with conditions before the advent of artificial light where elevated melatonin levels likely rose shortly after the setting of the sun and returned to dav-time levels about the time the sun rose above the horizon. In this scenario, all cells in the organism were exposed to much longer durations of elevated melatonin since, depending on latitude and season, the usual period of natural darkness far exceeds the period of darkness to which humans in modern societies are exposed. Hence, since humans are typically only in darkness during the interval when they sleep, their elevated circulating melatonin concentrations are of much shorter duration than if they lived in an environment without artificial light as occurred during the lengthy evolutionary period.

Because of the strong correlation between the length of the daily dark period and the duration of elevated blood melatonin levels (91), humans, compared to their pre-artificial light counterparts, must be considered relatively melatonin-deficient. This situation is made worse when, during the dark period, humans are acutely exposed to bright light. This rapidly inhibits pineal melatonin production, and circulating melatonin levels fall, further reducing the amount of melatonin cells are exposed to on a daily basis (92,93).

Since humans are usually only in darkness for the short interval they sleep during each 24-hour period (see the previous section on human sleep duration) melatonin levels in the blood are only elevated during the daily sleep period. It should be noted, however, that being asleep is not a requirement for elevated melatonin production; the only requirement is darkness. Thus, while melatonin has been shown to promote sleep (94,95), sleep is not a requirement for its endogenous synthesis. Given the short period of high melatonin levels in humans living in modern societies relative to what it was when humans were under natural photoperiodic conditions, humans in today's society are deficient in this important biogenic amine.

That melatonin influences the body weight of rodents seems well documented. For example, seasonal body weight changes in the Djungarian (dwarf) hamster (Phodopus sungorus) are clearly dependent on the pineal gland and the circadian melatonin cycle (96). During the short days of the winter, when the duration of nightly melatonin production is maximal, the body weight of this species declines. This drop in winter adiposity is prevented in pinealectomized (a procedure which eliminates the night-time rise in melatonin) hamsters and is reinstated by melatonin administration (97-99). In this species, a prolonged duration of the melatonin peak, which would normally be associated with a winter-type photoperiod, is critical in determining the ability of melatonin to adjust their body mass (99). Thus, longer daily melatonin production parallels a reduction in body weight.

In the rat, a species that has been more widely used to examine the effects of melatonin on body weight responses, the findings have often documented a slowing of body weight gain early in life (10,100-102) as well as a reduction in adiposity in older, obese animals when melatonin is given (103-106). Thus, when 2-month-old rats were provided melatonin in their drinking water for several months, this regimen reduced both the body weight gain (by roughly 25%) and the size of the perirenal visceral fat (by 50%) compared to animals that drank only water for the same period (10). These reductions, interestingly, were not accompanied by a commensurate lower food intake.

Some of the most interesting studies and those with the most significant outcomes are those in

which middle-aged, already fat animals were supplemented with melatonin. Thus, Walden-Hanson and co-workers (104) began their study with male Sprague Dawley rats that were, on average, about 520 g. When half of them were given melatonin in their drinking water, a significant reduction in body mass (to about 500 g) was already apparent within 2 weeks. This reduced body weight persisted for 14 weeks (compared to control rats not given melatonin, which continued to gain weight); at this time, the animals were crossed over. Within 4 weeks, the body weights of the two groups also crossed over, i.e. the rats that were previously the control animals lost weight while those now deprived of access to melatonin in their drinking water increased their body mass. Melatonin treatment also depressed intraabdominal adiposity and lowered plasma leptin and insulin to more vouthful levels. The body weight changes occurred even though the cross-over was not accompanied by an alteration in daily food consumption.

Some of the drugs used to treat schizophrenia, for example those referred to as atypical antipsychotics, often cause weight gain and augmented intraabdominal adiposity. Considering their success with previous studies in which melatonin reduced the body weights of middle-aged rats (103-106), Raskind and co-workers (101) tested whether the indoleamine would also limit body weight increases in young female rats treated with the atypical antipsychotic, olanzapine. Olanzapine is a chemical obesogen. Both melatonin and olanzapine were given in the drinking water and, as expected, those supplemented with the antipsychotic drug increased body mass more rapidly than the control animals drinking only water. The addition of melatonin clearly reduced body weight gain which was especially noticeable between 5 and 8 weeks of treatment (the study was terminated after 8 weeks). Similarly, the weight of the visceral fat (mesenteric, omental, perirenal, and retroperitoneal fat) was reduced in the melatoninsupplemented rats that received the drug. The changes measured were not accompanied by an alteration in food intake.

The ability of melatonin to limit body weight gain also is apparent when rats are fed a high-fat and high-cholesterol diet (100,106,107). As in several other published reports, melatonin's ability to restrain body weight gain in these studies was independent of energy intake. Differences in food intake definitely do not account for melatonin's efficacy as a weightreducing agent. Alterations in physical activity as a consequence of melatonin supplementation also do not explain the differential weight gain (10). Moreover, the differences seem not to relate to melatonininduced changes in either plasma testosterone, thyroxine, corticosterone, leptin, insulin, or IGF-1 (103,104).

Given the findings summarized above which show that elevated endogenous melatonin production and exogenously administered melatonin lower body weight along with the repeated observations that it does not alter total calorie intake, several authors have offered potential explanations as to how the indoleamine reduces body weight and intraabdominal adiposity. These explanations, however, are general and describe the outcomes to be a result of unidentified metabolic disturbances or alterations (50,103,106).

A recent study by Rios-Lugo and co-workers (108) also argues in favor of melatonin being protective against excessive weight gain both when rats are fed a normal diet as well as when they consume a high-fat diet. In the normal diet study, the addition of melatonin to the drinking water (25 µg/mL) resulted in the animals gaining roughly 25% less weight over a 9-week period; as in the previously discussed investigations, the differential weight gain was achieved without a difference in food intake between the two groups. In this study, melatonin consumption also significantly reduced mean plasma levels of insulin, glucose, and triglycerides which were measured at six time points over a 24-hour period. When the animals were fed a high-fat diet (35% fat), the effects of melatonin in reducing body mass were again apparent. Likewise, melatonin lowered circulating insulin, glucose, and adiponectin with less dramatic suppressive effects on leptin, triglycerides, and cholesterol. The authors interpreted their results to mean that, in addition to being a potentially useful agent to limit obesity, melatonin may be an effective add-in therapy to curtail insulin resistance and dyslipidemia in obese individuals (108).

Recently, we suggested the potential involvement of brown adipose tissue (BAT) as a factor whereby animals lose weight in response to melatonin administration (and gain weight when there is a deficiency of melatonin) without a commensurate reduction in food consumption (10). BAT has an uncommonly high metabolic activity and is responsible for nonshivering thermogenesis (109). These mitochondriarich cells burn large numbers of calories for the purpose of heat production, thereby limiting fat deposition. Melatonin, as reviewed above, induces weight loss (96–99); moreover, it stimulates the growth and metabolic activity of BAT (110-113). As a result, we feel that melatonin may have weightinhibitory effects due to its stimulatory actions on BAT (10). The stimulating actions of melatonin on BAT could explain the loss of weight and adiposity as seen in the studies where melatonin was administered to rodents, since they possess BAT deposits.

The findings related to melatonin and BAT could also have applicability to human weight control. Until recently it was thought that BAT was present in new-born but not adult humans (114). This was recently shown not to be the case, however. Using highly reliable methodologies, BAT was found to be widely disturbed in the trunk of humans, especially in the cervical and thoracic areas (115,116). As a result, we have proposed that melatonin may be a weight loss agent in humans as in rodents due to its ability to promote the growth and metabolic activity of BAT; a thorough description of the arguments supporting this assumption is provided in our recent review on this subject (10).

The Zucker diabetic fatty rat is a commonly used experimental model of metabolic syndrome since it develops early and progressive obesity, endothelial cell dysfunction, hypertension, dyslipidemia, and hyperglycemia (117). When melatonin was provided in the drinking water to obese Zucker rats, their body weight declined, lower serum triglycerides were measured, and HDL levels increased while LDL levels dropped (118). Systolic blood pressure, however, was not depressed in the melatonin-treated rats. Clearly, melatonin in this study positively influenced several metabolic parameters that are normally associated with metabolic syndrome. A rise in HDL values as a result of melatonin treatment has also been observed in the human (119).

In another model that had physiological features reminiscent of those of metabolic syndrome, rats were given melatonin (dose calculated to be 4 mg/kg daily) in their drinking water and were fed a normal or a high-fat diet for 16 weeks (120). The high-fat diet without melatonin supplementation caused increases in body weight, visceral adiposity, serum insulin, and triglycerides, all of which were prevented in the high-fat diet, melatonin-treated rats. In addition to these in-vivo measures, ex-vivo hearts were rendered partially ischemic (40 min ligation of coronary artery) followed by reperfusion (120 min) for the purpose of evaluating myocardial function, infarct size after ischemia/reperfusion, and molecular aspects of myocardial function. In the hearts from high-fat diet rats, melatonin significantly reduced infarct volume (by 58%) and improved functional performance. Also, during reperfusion, hearts from melatonin-treated rats showed activation of PKB/ Akt, ERK 42/44 and reduced p38 MAPK. The authors felt that the collective in-vivo and ex-vivo findings show that chronic melatonin administration protects against cardiac metabolic abnormalities in obese animals and also protects their heart from ischemia/reperfusion injury; activation of PKB/Akt and ERK 42/44 pathway may well have accounted for the protection provided by melatonin (120).

Recently, an open label study was carried out in which 30 adult humans diagnosed with metabolic syndrome were treated with 5 mg of melatonin nightly for 2 months (121). Melatonin was taken 2 hours before bedtime, and 33 healthy individuals served as controls. At the onset of the study, the metabolic parameters of the syndrome patients were changed as predicted relative to those measures in the control subjects. Even within the short interval of treatment (2 months), melatonin caused a significant improvement in the oxidative status (increased catalase activity and reduced levels of products of lipid peroxidation in red blood cells) along with a reduction in LDL cholesterol and a lowering of both systolic and diastolic blood pressure (121). Considering the significance of these findings it is essential that more studies of this type be performed in adult humans suffering with metabolic syndrome.

Although the number of studies is still limited and has been carried out primarily using rodents, the uniformity of the results suggests melatonin may well have anti-obesity effects even without a significant reduction in calorie intake; moreover, the indoleamine may reduce at least some of the symptoms of metabolic syndrome. With regard to the latter condition, as summarized herein, melatonin generally reduces insulin levels and fatness, and earlier studies in humans have reported that melatonin reduces mean blood pressure (56,122–125). These actions of melatonin along with its efficacy in limiting some aspects of cardiovascular disease should make this indoleamine an attractive agent as a potential treatment for obesity and metabolic syndrome (126–129).

Finally, the waning of the melatonin rhythm with advanced age, which occurs in all species where a potential association has been examined (130-133), may be one of several factors that contribute to the often gradual weight gain that is associated with middle age and beyond. As summarized in this report, melatonin has the capability of limiting white fat adiposity and, therefore, melatonin's loss would be expected to result in an increased body mass. Also, if in fact BAT is a factor in helping to control body weight, it is conceivable that those elderly individuals who also managed to maintain their youthful body size may have done so because, for genetic and/ or other reasons, they were able to maintain functional BAT deposits. Moreover, the body weightinhibiting effects of melatonin combined with its anti-diabetic actions, blood pressure-reducing effects, and cardioprotective actions could reduce the likelihood of developing metabolic syndrome. Considering the high safety margin of melatonin over a very wide range of doses, studies of this type should be initiated.

Concluding remarks

In the current review, we consider three factors that are speculated to contribute to obesity and its comorbidities: circadian disruption, sleep deficiency, and melatonin suppression. The evidence supporting each of these as being a potential contributor to fatness and metabolic disorders has accumulated primarily within the last decade (134-136). While it is convenient to investigate each of these features individually in relation to the obesity epidemic, they are in fact difficult to separate and obviously overlap and interact. Thus, in any study it is almost impossible to examine the impact of one of these potential causative factors individually without involving the others (53,136,137). More likely, these perturbations, along with other factors, conspire to enhance obesity and associated co-morbidities.

Circadian disruption, sleep deficiency, and melatonin suppression have at least one common causative feature, i.e. excessive light exposure including even brief periods of light at night. Indeed, interrupting the normal dark period with a short interval of bright light may be the most disruptive. Certainly, light pollution throughout the world, and especially in the economically well developed and developing nations, where obesity is also the most common, has become a major problem and is a serious concern. The use of artificial light after darkness onset in the evening and in the morning before sunrise is commonplace and impacts the physiology of the circadian system which influences both nocturnal melatonin synthesis and sleep. Moreover, being exposed to light after darkness onset due to what is referred to as trespass light or intentionally turning on a lamp is disruptive to the circadian system, which reduces melatonin levels and disturbs sleep. The persistent perturbation of the regular recurring light:dark cycle has already been, at least theoretically, linked to an increased cancer risk, particularly breast cancer (22-25,138) but possibly other cancers as well (139). We have recently proposed that not only cancer, but also obesity and its complications may be negatively influenced by repeated perturbations of the light:dark environment (9,10).

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