Sleep deprivation and circadian disruption in obesity and diabetes

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The earth rotates around its axis in approximately 24 hours, resulting in variation in exposure to light and temperature. Organisms have developed processes to enhance survival through anticipation of these variations. Thus, many biological processes follow approximately 24-hour (circadian) rhythms. Several organs have internal biological clocks (peripheral oscillators) that ensure maintenance of individual circadian rhythms. These clocks, whose molecular bases have been identified, are synchronised by the master clock (central oscillator) in the hypothalamic suprachiasmatic nucleus, which is adjusted or "entrained" by light signalled through the retinohypothalamic tract. When isolated from light or any other signals of time, organisms still maintain approximately 24-hour rhythms. Circadian processes ensure that the organism is ready for biological challenges throughout the 24-hour period.

The secretion of several hormones is determined by circadian rhythms. For example, cortisol levels rise before awakening and diminish as the time for sleep approaches. Leptin, an adipocytokine released by adipocytes to signal extent of fat stores, has higher levels at night during sleep compared with daytime. There are also 24-hour changes in levels of several metabolites, including glucose. Circadian rhythms also determine the timing of sleep and wakefulness.

Human social behaviours have increasingly challenged human biological systems. For example, shiftwork, particularly at night, results in circadian misalignment – that is, an asynchrony between the body's circadian rhythms and activities such as sleep. Shiftwork has been associated with the metabolic syndrome, obesity, diabetes, cardiovascular disease, cancer and increased mortality (Knutsson et al, 1986; Oberlinner et al, 2009). Metabolic disorders, in turn, can have deleterious effects on circadian rhythms, resulting in a vicious cycle (Boden et al, 1999). Shiftwork is also associated with sleep deprivation. While the deleterious metabolic alterations associated with shiftwork and their underlying mechanisms remain to be fully elucidated, circadian misalignment and sleep deprivation have been proposed as potential contributors to the current "pandemics" of obesity and diabetes.

Metabolic alterations as a result of circadian disruption and reduced sleep duration or quality or both have been repeatedly observed (Scheen and Van Cauter, 1998). There is strong evidence that decreased sleep duration and quality may have adverse effects on metabolic and endocrine function, which may result in future development of diabetes, obesity, the metabolic syndrome and cardiovascular disease.

In 1999, in a sleep laboratory study of healthy human volunteers, Spiegel and colleagues showed that a 4-hour sleep opportunity (sleep deprivation) for 6 nights was significantly associated with insulin resistance (Spiegel et al, 1999). The same group later demonstrated that restricting sleep duration to 4 hours per night for 2 consecutive nights was associated with decreased levels of leptin, and increased ghrelin levels, which together signal an energy deficit (Spiegel et al, 2004). Ghrelin is a stomach-derived hormone that signals hunger. Obesity is associated with high leptin levels due to leptin resistance; thus low leptin is a much more powerful biological signal than high leptin. Despite these studies providing a better understanding about the link between sleep deprivation and deleterious metabolic alterations, they included only a small number of young, healthy men in acute controlled laboratory conditions. Population studies, however, have demonstrated similar hormone alterations in habitually short sleepers (5–6 hours) (Taheri et al, 2004; Chaput et al, 2007).

Although some prospective studies have validated the cross-sectional data for associations between sleep duration and diabetes or obesity development (Gangwisch et al, 2007; Landhuis et al, 2008), others have investigated sleep parameters in those with pre-existing metabolic disease, such as diabetes (Knutson et al, 2006), and found that sleep debt or overall sleep quality (determined through the Pittsburgh Sleep Quality Index questionnaire) was associated with glycaemic control (HbA_{1c} levels) in those with and without diabetes complications. Thus, in some instances, there is a bidirectional relationship between sleep duration and metabolic dysfunction.

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Sleep stages and sleep timing also appear to play important roles for healthy metabolic function. In particular, slow-wave sleep (SWS) is associated with metabolic, neurophysiological and hormonal changes, all of which may potentially affect glucose equilibrium. Growth hormone (GH), for example, is closely coupled with SWS (Spiegel et al, 2000). Reduced SWS is associated with lower levels of GH, which, in turn, are associated with the metabolic syndrome. A recent experimental study demonstrated that suppression of SWS was significantly associated with 25% decreased insulin sensitivity, and glucose tolerance was reduced by 23% (Tasali et al, 2008), which was hypothesised to predispose to future development of type 2 diabetes mellitus. Similarly, recent epidemiological studies in older adults have shown cross-sectional and longitudinal relationships between napping and diabetes prevalence (Lam et al, 2010) and incidence (Xu et al, 2010), respectively. This suggests that sleep timing may be important since sleeping during the day opposes the body's natural biological rhythmicity and may subsequently disrupt hormone secretion.

A recent study by Buxton and colleagues examined 21 healthy adults for more than 5 weeks in strict laboratory controlled conditions simulating shiftworkers' sleep patterns (Buxton et al, 2012). The three-part study, in sequential order, followed a protocol of:

- Optimal baseline sleep with a 10-hour sleep opportunity.
- Three weeks of sleep restriction (5.6 hours of sleep opportunity within a 24-hour time period) coupled with circadian disruptions achieved by extending the 24-hour day to 28 hours (called forced desynchrony).
- Nine days of sleep recovery with circadian normalisation.

Throughout the study, light levels remained constant, ensuring that this did not reset circadian rhythmicity. The authors reported, at the end of the 3-week sleep and circadian disruption phase, a decreased resting metabolic rate and increased glucose concentrations subsequent to meal ingestion as a potential result of depleted pancreatic insulin release. The study also reported that these alterations were acute and normalised during the recovery phase of the study, suggesting that the occurrence was in response to sleep and circadian disruption. Scheer and colleagues also examined the impact of circadian misalignment on metabolic function using a forced desynchrony protocol (Scheer et al, 2009). They observed that circadian misalignment was associated with insulin resistance, low leptin and increased blood pressure. While these studies provide a better understanding of the processes that occur in shiftworkers and the impact that sleep loss and circadian disruption may have on metabolic function, the long-term effects (i.e. development of obesity and diabetes) still require further investigation.

The cross-sectional, prospective and experimental evidence is suggestive of an association between sleep deprivation and circadian misalignment and metabolic dysfunction. Conversely, there is also an association between long sleep duration and metabolic abnormalities (Arora et al, 2011), which requires further investigation. Emerging research not only highlights a need to review the impact of societal practices on sleep and circadian rhythms with downstream deleterious health outcomes, but could also identify new targets for treatment of common conditions such as obesity and diabetes. ■

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