The Suprachiasmatic Nucleus, Circadian Clocks, and the Liver

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The circadian clock system adapts phasic physiological activities, such as sleeping and eating, to environmental cycles. The "master clock" is in the suprachiasmatic nucleus (SCN) and the principal cue (Zeitgeber) is the light–dark cycle, around which most mammalian (and those of all living organisms) functions have evolved. In our society, with activity 24 h per day, the clock is frequently overridden or does not match the activity schedule, with increased susceptibility to disease (obesity, type 2 diabetes, and their cardiovascular sequelae) resulting.

MOLECULAR CLOCKS

In the SCN and in other cells, the core molecular clock mechanism consists of specific genes ("clock" genes). These include *Clock* (and *Npas2)*, *Bmal*, the period homologs, *Per1* and *Per2*, and cryptochrome 1 (*Cry1*) and *Cry2*. The circadian clock mechanism revolves around transcription–translation feedback loops, in which repression and activation of transcriptional activity are dependent on dimerization, posttranslational modification, and degradation rate constants that define the reactions. Kinetically (in conjunction with a secondary feedback loop comprising nuclear receptor genes, *Reverbs* and *Rors*), this system defines an oscillator with a period that is near 24 h (1,2). Photic cues channeled via the SCN fine-tune the period to correspond to that of the environment. Information on this period is then transmitted to the periphery. The same molecular clocks are also found in peripheral cells (e.g., kidney, liver, pancreas). They can function autonomously. However, the master clock in the SCN generally coordinates these peripheral clocks by way of the autonomic or humoral (e.g., corticosteroids, melatonin) routes to generate a synchronized signal that aligns metabolic and other activities with environmental conditions (1,3).

SLEEP

Sleep–waking cycles are clearly set by the light–dark cycle. Disrupted sleep patterns impose alterations in this cycle. As, for example, with jet lag, the circadian clock adapts to these changes (4). There is now a great deal of literature on disordered sleep and metabolic disorders (5). Thus, obstructive sleep apnea and sleep deprivation are implicated in insulin resistance or the entire metabolic syndrome (6,7). Interestingly, there is some evidence that the state of malnutrition that can be induced by some eating disorders and its attendant altered metabolism also have effects on sleep patterns (8). There is thus a reciprocity in the effects of circadian rhythms and sleep on each other, as well as those of sleep on metabolism. Therefore, sleep may, to some extent, act as a filter by which the circadian clock exerts its effects on metabolism (Fig. 1*A*).

MEALS

Meals provide another such filter. Feeding behavior in rodents is clearly dependent on the central clock. SCN lesions disrupt the light–dark cycle feeding patterns as shown, for example, by Coomans et al. (9). Similar effects are achieved with individual clock protein null mutations (3). Under conditions of restricted feeding, altering feeding patterns also can override the coordinating signals from the SCN (10) and entrain food anticipatory behavior (11,12). Meal consumption at inappropriate times (such as during the night–sleep cycle) can lead to the metabolic changes of obesity. Such observations demonstrate the reciprocal nature of the signals between circadian clocks and meal patterns in humans or feeding behavior in rodents (Fig. 1*A*).

Sleep, meals, and other behavior are both regulated by the circadian clock and can entrain circadian rhythms. Disturbances in sleep and eating behavior also affect metabolism, thus transmitting a "filtered" version of the signal from the SCN. A large number of proteins in peripheral tissues, the liver being prominent among them, are expressed in a cyclic fashion in accordance with circadian rhythms. In rodents this translates into diurnal rhythms in hormones and metabolites such as glucose (13). In humans, blood glucose concentrations remain stable during fasting in most studies (14). How, then, does the SCN interact with glucose metabolism, specifically its liver metabolism?

SCN AND LIVER GLUCOSE METABOLISM

The article by Coomans et al. (9) provides an interesting and important insight into this issue. A selective ablation of the SCN (SCNx) in mice was compared not only to sham-operated animals but also to those with collateral damage in the paraventricular nucleus (PVN; unilateral or bilateral) or in both the PVN and the ventromedial hypothalamus (VMH), in addition to SCNx. These were carefully categorized and grouped. SCNx animals demonstrated a cessation of circadian activity, feeding, and oxygen consumption, with a small increase in glycemia as well as body mass attributable to accretion of fat. Somewhat surprisingly,

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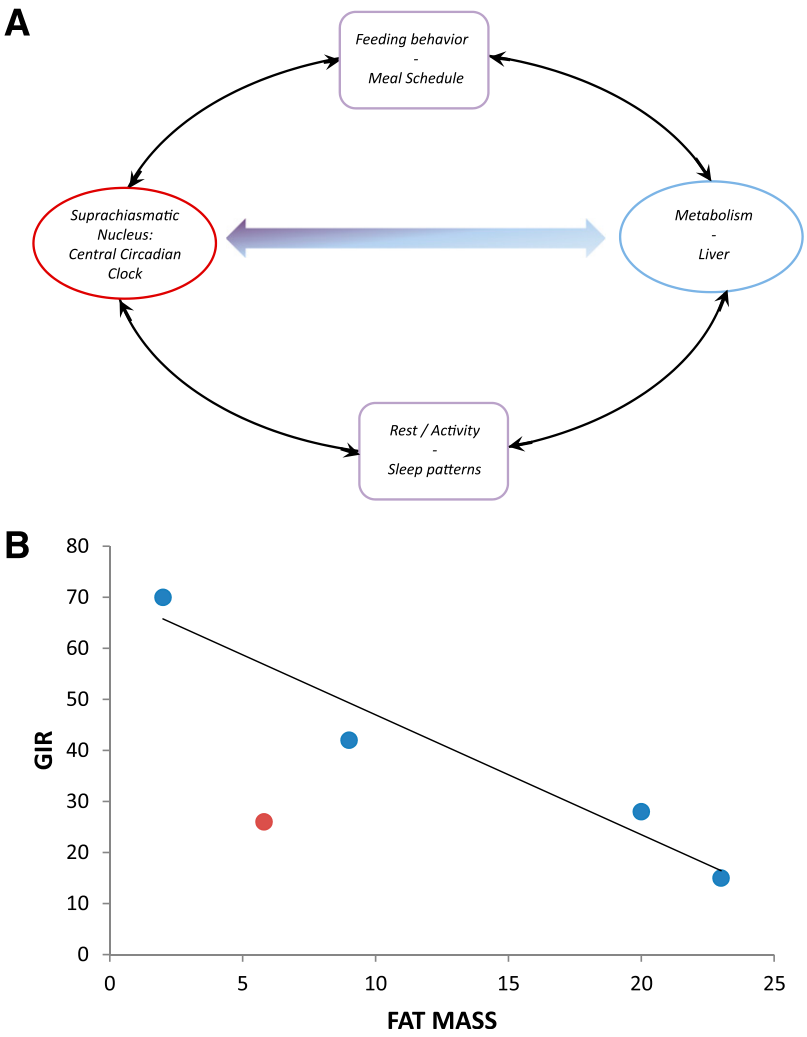

FIG. 1. *A*: Schematic of some of the reciprocal interactions in the control of metabolism by circadian clocks and vice versa. *B*: Plot of data from Coomans et al. (9) showing insulin sensitivity as represented by the GIR during a hyperinsulinemic isoglycemic clamp compared with the fat mass. Blue circles represent data from shams and animals with unilateral or bilateral lesions of the PVN and lesions of the PVN plus VMH as well as of the SCN. The red circle represents selective ablation of the SCN alone.

tracer-based measurements also showed a selective and profound decrease in the suppression of endogenous/hepatic glucose production during a hyperinsulinemic isoglycemic clamp and, therefore, a parallel decrease in hepatic insulin sensitivity. This decrease accounted for almost the entire decrease in the glucose infusion rate (GIR) during the clamp, which is a measure of the insulin sensitivity.

When the damage was expanded to include adjacent areas of the hypothalamus (PVN with or without VMH), fat (and body) mass increased proportionally to the extent of the lesion, glycemia increased marginally, and the circadian activity and food intake patterns remained lost. Basal insulinemia increased proportionally to the increase in fat mass. GIR and hepatic insulin sensitivity decreased in synchrony. The linear decline of GIR with fat mass in the animals with extended (beyond the SCN) lesions is illustrated in Fig. 1.

It is interesting that the GIR in the mice with selective SCNx is clearly an outlier with a much more profound decrease in GIR relative to the increase in fat mass. This observation suggests the following:

1) There is a direct effect of the SCN (and therefore its ablation) on hepatic insulin sensitivity/glucose production. This would be consistent with the neural/autonomic pathway elegantly demonstrated by the same Amsterdam laboratory using viral tracing techniques (15). The effect of the SCNx on the liver may well be independent of its function as the central clock.

2) Lesions on the PVN/VMH modulate the effect of SCNx on the liver and appear to attenuate it. These areas are critical in energy homeostasis, and this function appears to override the SCN regulation, so that the gain in fat mass is primary and the increase in insulin resistance appears to occur after this increase in weight in a manner analogous to that resulting from weight gain by other pathways.

The disruptions of circadian rhythms are maintained across the spectrum of lesions that were applied. Only the effects on the fat mass and on the liver are altered, suggesting a differential mechanism for this effect of SCNx. The extent to which this effect might be dependent on the clock function of the SCN therefore remains to be determined. However, evidence is presented here indicating that control of liver metabolism at the level of the SCN is modifiable.

LIVER GLUCOSE METABOLISM AND DIURNAL RHYTHMS

It is now accepted that dissociation of behavioral patterns from environmental rhythms may lead to obesity and type 2 diabetes, as well as cardiovascular sequelae. It is interesting to consider some changes in diurnal rhythms that have been noted in diabetes (16). Nondiabetic individuals (14) and some mouse models (17), whether lean or overweight, maintain a constant fasting glycemia over a diurnal cycle (14,16), although drifting downward with extended fasting. Compared with BMI- and age-matched individuals, subjects with type 2 diabetes who were fasting demonstrated a cyclic pattern of glycemia over a 24-h period. Lowest glucose levels were observed in the evening and they increased throughout the night to reach highest levels at ~7:00 A.M. Tracer-determined estimates of flux rates showed that the diurnal changes in glycemia that occurred were driven by changes in glucose production, specifically gluconeogenesis. This could be explained by the following:

1) Disruptions in the SCN central clock. This would be supported by the large delay and decrease in melatonin secretion observed.
2) Melatonin itself possibly affecting glucose metabolism (18). This is further supported by genome-wide association studies implicating a melatonin receptor in hepatic insulin resistance, impaired insulin secretion, and increased type 2 diabetes risk (19).
3) Transition to an oscillatory behavior of metabolic systems when appropriate changes occur in rate constants describing these systems. Such biochemically induced oscillations could be considered as similar to those generated by cellular clock mechanisms.

Because, in diabetes, it is the putative disruptions in the SCN, the biological clock, or melatonin secretion that were coupled with the appearance of new cyclic behavior, the third hypothesis became more likely. The implications of this proposition would be that cycles or oscillations can be generated at the metabolic level, and that these could be imposed on the central biological clock, which is modifiable (as discussed). There is previous evidence that alterations in metabolism (20) could affect such changes. It is also interesting that the liver may have a dominant role in entraining the expression of many peripheral clock genes, overriding central influences (21). Such a relationship would complete the reciprocal influences of the SCN and its targeted metabolic pathways shown in Fig. 1. Moreover, it could be mediated through changes in peripheral clock proteins. Its importance would be reflected in the direct association with disease etiology.

The article by Coomans et al. (9) demonstrates the pervasive control of the SCN on circadian rhythms in metabolism. It also finds a direct and profound effect on hepatic insulin sensitivity, which appears to be modulated by collateral lesions to the PVN and VMH. In a reciprocal relationship, the liver, too, may play an important role in modulating central clock effects. Such interactions between the complex networks represented by the "metabolome" and the "chronome" may determine the plasticity of the system, allowing adaptation to its environment as well as the susceptibility to, and even the transition to, disease states such as type 2 diabetes.

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