Circadian disruption in the pathogenesis of metabolic syndrome

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Received 11 September 2013; received in revised form 15 December 2013; accepted 16 December 2013

Abstract

Metabolic syndrome is a multifactorial process induced by a combination of genetic and environmental factors and recent evidence has highlighted that circadian disruption and sleep loss contribute to disease pathogenesis. Emerging work in experimental genetic models has provided insight into the mechanistic basis for clock disruption in disease. Indeed, disruption of the clock system perturbs both neuroendocrine pathways within the hypothalamus important in feeding and energetics, in addition to peripheral tissues involved in glucose and lipid metabolism. This review illustrates the impact of molecular clock disruptions at the level of both brain and behavior and peripheral tissues, with a focus on how such dysregulation in turn impacts lipid and glucose homeostasis, inflammation and cardiovascular function. New insight into circadian biology may ultimately lead to improved therapeutics for metabolic syndrome and cardiovascular disease in humans.

Keywords: Metabolism; Circadian rhythm; Cardiovascular disease

1. Metabolic syndrome: etiology

Metabolic syndrome (MetS) is defined by several phenotypic abnormalities, including central (intra-abdominal) obesity, dyslipidemia (elevated triglyceride, and reduced high-density lipoprotein cholesterol), impaired glucose tolerance, and hypertension. Elevated circulating inflammatory and/or thrombotic markers (C-reactive protein, tumor necrosis factor-α, interleukin-6, and plasminogen activator inhibitor type 1) or reduced levels of anti-inflammatory molecules such as adiponectin have also been associated with MetS [1,2]. This syndrome has become a public health challenge worldwide; an estimated 25 to 40% of individuals between the ages of 25 and 64 years of age have MetS (San Antonio Heart Study) [1,3–6]. Moreover, a recent systematic review and meta-analysis, involving over 950,000 patients with MetS, estimated a 2.3 fold increased risk in cardiovascular disease (CVD) and a 2.4 fold increase risk in CVD mortality [7]. Furthermore, in the same report, patients with MetS, but without type 2 diabetes mellitus, maintained a high cardiovascular risk. It is established that body fat distribution rather than adiposity per se is a key feature of the syndrome. Excess of intra-abdominal fat rather than subcutaneous (sc) fat (central vs. peripheral obesity) is associated with MetS and CVD [5,8].

The increased adoption of calorically dense (high fat and high carbohydrate) diet, in addition to genetic susceptibility, both contribute to the emergence of the MetS [1]. Consequently, current public health surveys of human nutrition have focused on the macronutrient composition of diet. For instance, recently, Estruch et al. document that provision of extra-virgin olive oil or mixed nuts, in the context of a Mediterranean-style diet, substantially reduced the occurrence of CVD [9]. Such diets are rich in total monounsaturated and polyunsaturated fat and are lower in saturated fat. Another area of recent interest is vitamin D. Increasing evidence indicates that vitamin D deficiency (from sun exposure and/or dietary sources) is associated with multiple parameters of MetS [10–14].

In addition to poor quality of nutrition, excess food intake and physical inactivity, sleep disturbance impacts on metabolism. Indeed, numerous cross-sectional, as well as prospective clinical, studies have demonstrated that short-duration and poor-quality sleep predicts the development of type 2 diabetes and obesity even after age, body mass index and various other confounding variables are taken into account [15–17]. Moreover, shift work is linked to increased risk of type 2 diabetes [18,19] and stroke [20]. Surprisingly, it has been observed that sudden changes in the biologic rhythm can lead to adverse effects on cardiovascular health. For instance, shifts
to daylight saving time in spring have been associated with an increased incidence of myocardial infarction [21].

Finally, new perspectives into the understanding of MetS pathogenesis can be derived from studies of experimental animal models demonstrating that feeding time also dramatically impacts the development of the MetS [22–28]. When feeding a high-fat diet (HFD) is restricted to the active (dark) phase, mice consumed equivalent calories to those with ad lib access and yet are protected against obesity, hyperinsulinemia, hepatic steatosis, and inflammation [23]. Furthermore, other studies showed that the abnormal feeding rhythm corrected by scheduled feeding rescues the onset of obesity in HFD-fed mice [24,29] and as well as in a genetic model of hyperphagia with a dysregulated feeding rhythm, such as in Histamine-H1(R)-R knockout mice (H1KO) [25]. Conversely, mice fed a HFD only during the 12-hour light phase gain significantly more weight compared to isocalorically fed mice that were provided food only during the 12-hour dark phase [22]. Similarly, disruption of the normal light/dark cycle (by exposure of mice to light during the night or housing mice in 20-h light/dark cycles), simulates shift work disruption or jet lag in humans, disrupts the timing of food intake, and results in accelerated weight gain [27,30]. Remarkably, restricting food consumption to the active phase in mice exposed to light during the night prevents body mass gain [27]. Such a relationship between temporal pattern of food intake and the development of metabolic disruptions has been suspected in human, but remains poorly characterized [31]. Nevertheless, a causal link between circadian misalignment and metabolic homeostasis has been described [32]. Indeed, when subjects ate and slept 12 hours out of phase from their habit-

Fig. 1. Core molecular clock. The core molecular clock in mammals is expressed both in brain and peripheral metabolic tissues and coordinates behavioral (i.e. sleep-wake, feeding-fasting), endocrine and metabolic responses with the light/dark cycle. The core molecular clock is composed of a feedback loop involving a series of activators (CLOCK/BMAL1) and repressors (CRYs/PERs) that generate ~24 hours rhythms of gene transcription. CLOCK/BMAL1 activate the rhythmic transcription of downstream target genes that contain E-box cis-regulatory enhancer sequences, including the Per and Cry genes. The non-phosphorylated proteins PER and CRY heterodimerize, translocate to the nucleus, and inhibit CLOCK/BMAL1. Phosphorylation, in turn, targets PER–CRY for ubiquitin-mediated proteolysis. In addition, CLOCK–BMAL1 activates transcription of the retinoic acid-related orphan nuclear receptors Rev-erba and Rora genes. In turn, REV-ERBα represses, while RORα activates, Bmal1 transcription. During the dark phase, CK1ε and CK1β phosphorylate PER and CRY, tagging them for ubiquitylation by FBXL3, and leading to their degradation by the proteosome. BMAL1: brain and muscle aryl-hydrocarbon receptor nuclear translocator-like 1; CLOCK: circadian locomotor output cycles kaput; CK1ε and CK1β: casein kinase 1ε and β; Cry1: cryptochrome 1; FBXL3: F-box and leucine-rich repeat protein 3, Per2: Period 2; ROR: retinoic acid-related orphan receptor.

Adapted from Bass [35].
ual times, circadian desynchrony decreased leptin levels and resulted in hyperglycaemia and hyperinsulinemia. In addition, arterial pressure was elevated and some of the subjects also exhibited postprandial glucose responses comparable to those of a prediabetic state [32]. In another recent study, 420 overweight/obese patients undergoing a 20-week weight-loss diet, those who ate their main meal late lost significantly less weight than early eaters, independently of their daily caloric intake [33]. Nevertheless, in these experimental human studies, it is hard to distinguish the effect of circadian disruption from the effect of sleep quantity and quality, feeding time, and/or interindividual variation in chronotype. Despite the multifactorial nature of MetS, genetic animal models provide the opportunity to isolate and dissect the interconnections between circadian systems and metabolism. A goal of this review is to highlight insight gleaned from genetic animal models into how altered energy homeostasis, lipid and glucose homeostasis, inflammation and cardiovascular function may be tied to circadian dysregulation.

2. Core molecular clock

Circadian timekeeping is a ubiquitous feature of all animals and allows appropriate temporal regulation of an organism’s internal metabolism to anticipate and respond to recurrent daily changes in the environment. Genetic and biochemical studies have shown that the molecular clock is comprised of a feedback loop encoded by transcriptional activators (CLOCK/BMAL1) that activate repressors (PERs/CRYs) that feedback to inhibit their activity in a cycle that repeats itself every 24 hours (Fig. 1). In addition to the primary feedback loop, a second negative feedback loop involving the nuclear hormone receptors, REV-ERBα and β (and RORα, act through an RRE within the Bmal1 promoter to repress and activate its transcription, respectively (Fig. 1). This short feedback loop is thought to stabilize the forward limb of the clock. A variety of post-transcriptional events participate in sustaining the 24 hr rhythm, including regulation of protein stability through phosphorylation of the core clock repressors, followed by ubiquitin-mediated degradation, and RNA processing impacting translational efficiency of clock factors (for review [34]).

Internal circadian synchrony is entrained to the solar cycle via the suprachiasmatic nucleus (SCN). Light input is transmitted to the clock through the retinal melanopsin neurons, which project via the retinohypothalamic tract to the SCN [36]. Peripheral cells express the full repertoire of core clock proteins and exhibit self-sustained oscillation ex vivo when entrained to a pulse of serum, temperature, or cyclohexanedione. Feeding derived humoral signals entrain peripheral clocks in liver [37], in addition to additional signals including autonomic innervation and temperature (for review [38]).

The discovery of this molecular loop, and the finding that clock genes are expressed both within pacemaker neurons in brain and in peripheral cells of endocrine pancreas, liver, adipose tissue and immune system, opens the opportunity to exploit genetic strategies to disrupt the molecular function of the clock

<table>
<thead>
<tr>
<th>Mouse model</th>
<th>Metabolic and/or endocrine phenotype</th>
<th>Diurnal and/or circadian phenotype</th>
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<tbody>
<tr>
<td>Bmal1−/−</td>
<td>Increased adiposity at early ages, obesity [43–45]; hyperlipidemia [46]; disruption of circadian variation in blood pressure and heart rate, [69]</td>
<td>Arrhythmic [50]</td>
</tr>
<tr>
<td>ClockΔ19</td>
<td>Hyperphagia early in life, with subsequent development of hyperlipidemia, hyperleptinemia, hepatic steatosis and hypoinsulinemic hyperglycaemia [51–53]</td>
<td>4 h longer period followed by arrhythmia [54]; increased daytime feeding [51]</td>
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<tr>
<td>Per2−/−</td>
<td>Increased weight gain on high-fat diet [55]</td>
<td>1.5 h shorter period followed by arrhythmia [56]; increased daytime feeding [55]</td>
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<tr>
<td>Cry1−/−; Cry2−/−</td>
<td>Hyperglycaemia, impaired glucose tolerance [57,58]; increased inflammation upon LPS challenge [59]; hypertension [60]</td>
<td>Arrhythmic [61,62]</td>
</tr>
<tr>
<td>Adipocyte Bmal1−/−</td>
<td>Obesity, lower energy expenditure [63]</td>
<td>Increased daytime feeding [63]</td>
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<tr>
<td>Hepatocyte Bmal1−/−</td>
<td>Fasting hypoglycaemia and enhanced glucose clearance [43]</td>
<td>Normal circadian activity and feeding rhythms</td>
</tr>
<tr>
<td>Pancreas Bmal1−/−</td>
<td>Hyperglycaemia, impaired glucose tolerance [53,64,65]</td>
<td>Normal circadian activity and feeding rhythms</td>
</tr>
<tr>
<td>Myeloid cells Bmal1−/−</td>
<td>Increased expression of monocyte-attracting chemokines [66], increased systemic inflammation, hepatic steatosis, insulin resistance and hyperglycaemia on high-fat diet [66]</td>
<td>Normal circadian activity and feeding rhythms</td>
</tr>
<tr>
<td>Rev-erba−/−</td>
<td>Dyslipidemia [67,68]; disrupted temporal gating of endotoxin-induced inflammation [49]; reduced mitochondrial content and oxidative function, as well as upregulation of autophagy in muscle [69]</td>
<td>0.5 h shorter period [70]</td>
</tr>
<tr>
<td>Rev-erba−/−; Rev-erbβ−/−</td>
<td>Increased circulating glucose and triglyceride levels, and a reduction in the level of free fatty acids in inducible double mutants [70]</td>
<td>2.5 h shorter period in inducible double mutants [70]</td>
</tr>
</tbody>
</table>
system in diseases including diabetes and cardiometabolic syndrome. Early transcriptome profiling pointed towards a tight connection between metabolism and circadian clocks [39–42]. Between 3–21% of the transcriptome is expressed in circadian pattern, with an enrichment of cycling factors involved in biosynthetic and metabolic pathways, including cholesterol and lipid metabolism, glycolysis and gluconeogenesis, oxidative phosphorylation and xenobiotic detoxification.

3. Clock disruption and metabolic syndrome

Evidence to support a role of the circadian clock in the regulation of energy homeostasis, lipid and glucose metabolism, inflammation and cardiovascular function has been strengthened by genetic studies in animal models with mutations in core components of the circadian clock (Table 1).

3.1. Circadian clock and energy homeostasis

Homozygous ClockΔ19 mutant mice, which display a loss of circadian activity rhythm in constant darkness [54], have yielded insight into understanding the role of the clock network in energy homeostasis and provide evidence that circadian clock disruption leads to metabolic abnormalities. In addition to disruption in sleep and circadian behavior, these mutant mice are obese and hyperphagic, and subsequently develop features of the MetS, including hyperlipidemia, hyperleptinemia, and visceral adiposity. In addition, they also develop hypoinsulinemic hyperglycaemia [51]. These mice show a dampened feeding rhythm, with increased food intake during the day, and an overall increased food intake.

Bmal1−/− mice display a complete loss of circadian rhythmicity in constant darkness associated with increased adiposity at early ages [43], a phenotype that may arise in part due to effects within peripheral adipose tissue [46,71,72]. Indeed, Bmal1−/− mice develop arthropathy and myopathy [46,72], while muscle rescue restored normal activity and body weight in these mice [71]. In addition, when challenged with a HFD, Bmal1−/− mice were obese prone [44], Per2−/− mice also gain more weight than wild-type mice when fed a HFD [55]. These mice lose the normal diurnal pattern of feeding, eating as much during the light period as they do during the dark period when fed a HFD [55]. Collectively, these data suggest that disruption of clock gene expression impacts energy homeostasis due to effects within both brain and peripheral tissues on both behavior and cellular metabolism in mice.

Finally, the original ClockΔ19 mutant and other clock mutants were developed and usually characterized in the C57BL/6J strain. However, mutant phenotypes associated with clock disruption can differ with genetic background. For example, when introgressed onto the ICR strain, the ClockΔ19 mutation results in impaired dietary fat absorption and thus Clock mutation attenuates obesity induced by a high-fat diet in mice with an ICR background [73]. Another unique aspect of the C57BL/6J strain is that it is melatonin-deficient. Melatonin effects can be studied by introgression of the ClockΔ19 mutation into the CBA strain [74].

In addition to these findings in animal models, mounting evidence suggests that genetic variation in circadian genes also influences fat accumulation in humans. For example, in small sample populations, polymorphisms in the CLOCK gene have been associated with predisposition to human obesity [75,76] and PER2 polymorphisms with abdominal obesity [77].

3.2. Circadian clock and lipid metabolism

Genetic loss or mutation of core clock genes also leads to specific alterations in adipocyte biology and lipid homeostasis. Levels of adipokines such as adiponectin [78] and leptin [79] exhibit circadian variation, while ablation of Bmal1 abrogates differentiation of embryonic fibroblasts into adipocytes [80]. Furthermore, circadian modulation of lipolysis regulates the availability of lipid-derived energy during the day, as revealed by profiling blood and adipose tissue samples from wild-type, ClockΔ19 mutant and Bmal1−/− mice [81]. Diurnal variations in lipolysis rates and release of free fatty acids and glycerol into the blood are correlated with rhythmic regulation of the adipocyte clock [81].

Adipocyte-specific deletion of Bmal1 results in obesity in mice with a shift in the diurnal rhythm of food intake, possibly related to altered rhythms of adipokine production [63]. Adipocyte from these mutant mice also showed a reduced number of polyunsaturated fatty acids in triglycerides, leading to decreased circulating polyunsaturated fatty acids and non-esterified polyunsaturated fatty acids in hypothalamic neurons that regulate food intake [63]. Thus, expression of the peripheral circadian clock in adipocytes influences entrainment of feeding rhythms to the light-dark cycle due to actions within the central nervous system.

Both intestinal lipid transport and de novo lipid synthesis also exhibit circadian variation [82]. Hypertriglyceridemia is evident in ClockΔ19 and Bmal1−/− mutant mice [51], likely due to both intestinal overabsorption [83] and hepatic overproduction [46,52]. The link between circadian clock and transcriptional control of lipogenesis was made in genomic studies of Rev-erba, demonstrating that this factor colocalizes with histone deacetylase 3 (HDAC3) near genes regulating lipid metabolism, and that deletion of HDAC3 or Rev-erba in mouse liver causes abnormal hepatic lipogenesis [70,84,85]. These findings are consistent with previous observations showing that REV-ERB participates in circadian sterol regulatory element–binding protein (SREBP) signaling and bile acid homeostasis [67,68]. Moreover, chronic exposure to REV-ERB agonists alters circadian expression of key genes involved in lipid storage in adipose tissue, modulates lipogenesis and cholesterol/bile acid synthesis in the liver, and increases lipid and glucose oxidation in the skeletal muscle [86]. The improvement of plasma triglycerides and cholesterol levels induced with synthetic REV-ERB ligands, suggests that this pathway may provide a therapeutic avenue for treatment of dyslipidemia in humans [86].

3.3. Circadian clock and glucose homeostasis

In addition to the effect of clock on lipid metabolism, glucose tolerance and insulin action also oscillate in a diurnal fashion.
The SCN has been described to play a critical role in this process [87,88]. Indeed, ad libitum glucose levels and glucose tolerance are known to peak before the onset of the active period compared with the rest phase [87,88]. This peak of glucose is likely due to increased hepatic gluconeogenesis [88] and low insulin secretion [89]. On the other hand, the improved glucose tolerance is believed to be attributable to elevated glucose uptake at skeletal muscle and adipose tissues [87,90].

Genetic models confirmed the strong involvement of clock genes in mediating glucose homeostasis. Clock\(^{α19}\) mutant mice develop age-dependent hyperglycaemia and hypoinsulinaemia [53], in part due to impaired insulin secretion and defects in proliferation of pancreatic islets. In addition, deletion of Bmal1 within pancreas causes hyperglycaemia and hypoinsulinaemia [53,64,65]. However, mice with a liver-specific deletion of Bmal1, exhibited hypoglycaemia restricted to the fasting phase of the feeding cycle and loss of rhythmic expression of hepatic glucose regulatory genes [43]. In liver, Cry1 expression is elevated during the night-day transition and reduces fasting gluconeogenic gene expression [57]. Cry1\(^{-/-}\) and/or Cry2\(^{-/-}\) mice display glucose intolerance [58]. The mechanism linking CRY to glucose homeostasis is still under study and may involve either effects on cyclase signaling and/or transcription [58,91].

In addition to these effects of clock gene disruptions in liver and pancreas (described above), a new study demonstrated the impact of Rev-erba in glucose homeostasis in skeletal muscle [69]. Indeed, Rev-erba is highly expressed in oxidative skeletal muscle and its deficiency in muscle leads to reduced mitochondrial content and oxidative function, as well as upregulation of autophagy [69].

Interestingly, genetic variation of circadian genes in humans is correlated with glucose homeostasis. For example, a genomic-association study in nonobese diabetic participants indicated that Cry2 gene variants are associated with glucose levels [92]. In a smaller cohort, polymorphisms within Per2 have also been associated with high fasting blood glucose [93]. Furthermore, carriers of the CLOCK SNP rs4580704 display lower glucose levels and improved insulin sensitivity only when on a diet high in monounsaturated fatty acids [94].

3.4. Circadian clock and inflammation

The circadian system regulates inflammatory pathways that contribute to the development of MetS. Mounting evidence suggests that immune function varies throughout the day [95]. In mice, spleen, lymph nodes, and peritoneal macrophages contain intrinsic circadian clockworks that oscillate autonomously even ex vivo [96]. At the molecular level, >8% of the macrophage transcriptome are expressed in circadian fashion, including many important regulators for pathogen recognition and cytokine secretion [96]. Interestingly, a new study provided evidence that REV-ERBs regulate macrophage gene expression by repressing transcription from enhancers that are selected by macrophage-lineage-determining factors [97]. In intestinal epithelial cells, Toll-Like Receptors (TLR) expression, a family of pattern-recognition receptors that play a critical role in the innate immune system, is also under circadian control and enables microbiota cues to be transduced [98]. Furthermore, NF-κB activation in response to immune challenge, such as a bacterial lipopolysaccharide (LPS) administration through TLRs, display daily variation, with a maximum activation at ZT6 during the rest period and a minimum activation at ZT18 during the active period indicating that NF-κB activation is under circadian control [99]. The circadian clock also modulates the inflammatory response during acute infection with the pathogen Salmonella with highest pro-inflammatory response during the early rest period for mice [100]. Circadian gating of endotoxin response was lost in Bmal1\(^{-/-}\) and Rev-erba\(^{-/-}\) mice [49] and lack of CRY constitutively activates the pro-inflammatory cytokines in Cry1\(^{-/-}\) and Cry2\(^{-/-}\) double mutant mice [59]. Remarkably, in addition to the monocytes and to a higher expression of chemokines induced by a myeloid cell-specific deletion of Bmal1, the mice carrying such a mutation also showed an increased infiltration of monocytes in the adipose tissue, increased weight gain, ectopic deposition of triglycerides in liver, and insulin resistance when fed a HFD [66]. This study suggests that disruption of the diurnal rhythms of monocytes might potentiate metabolic inflammation and disease [66]. Since obesity and lipid overflow result in conditions that promote a pro-inflammatory state in metabolic tissues including adipose tissue, liver, skeletal muscle but also in the hypothalamus [101–103], a better understanding of the role played by circadian control of inflammatory pathways on MetS pathogenesis would be beneficial.

3.5. Circadian clock and cardiovascular function

In humans, the onset of various pathological events associated with MetS, such as stroke, myocardial infarction, arrhythmia and sudden cardiac death, has been shown to peak in the early morning. Temporal variations in the production of glucocorticoids, catecholamines, aldosterone, angiotensin II, and endothelial NO synthase (eNOS) activity, is partially responsible for diurnal regulation in vascular reactivity, resulting in the diurnal rhythm of blood pressure (for review [104]). Indeed, Clock\(^{-/-}\) mice exhibit disrupted renal sodium reabsorption and reduced arterial blood pressure [105]. Similarly, arrhythmic Cry1 and Cry2 double mutants (Cry1\(^{-/-}\); Cry2\(^{-/-}\)) suffer from salt-sensitive hypertension due to abnormally high synthesis of the mineralocorticoid aldosterone by the adrenal gland [106]. Furthermore, overexpression of the Clock\(^{α19}\) allele in cardiomyocytes alters heart rate variability and contractility [107]. In addition, the circadian variation in blood pressure and heart rate is disrupted in Bmal1\(^{-/-}\), and Clock\(^{α19}\) mutant mice [47] and as well as endothelial cell-specific PPAR\(^{γ/-}\) mice, which are shown to have reduced Bmal1 expression [108]. Cardiovascular phenotype in these clock mutant mice may be partially explained by an altered diurnal variation in catecholamines [47]. To that end, it has been shown that Perl regulates sodium balance through modulating the expression of the renal epithelial sodium channel [109] and Bmal1 is involved in coupling of eNOS, production of superoxide, and maintenance of endothelial function [48,110]. Circadian clock function is also necessary for physiological fibrinolysis and thrombogenesis. For instance, plasminogen
activator inhibitor type 1 (PAI-1), the major physiologic inhibitor of tissue-type plasminogen activator in plasma, peaks in the early morning, explaining, at least in part, the occurrence of hypofibrinolysis and of the temporal variation in thrombosis [111]. In ClockΔ19 mutant mice, the lower plasma PAI-1 levels is associated with a significantly longer time to thrombotic vascular occlusion while Bmal1−/− mice present a shorter time to thrombotic vascular occlusion [112]. As another example, the diurnal expression of the thrombopoietin gene, whose disruption may contribute to cardiovascular disease [113,114], is also altered in ClockΔ19 mutant mice [115]. Interestingly, in a small human cohort, 2 BMAL1 haplotypes have also been associated with type 2 diabetes and hypertension [116].

4. Conclusion

Emerging work in experimental genetic models has provided insight into the mechanistic basis for clock disruption in disease. Indeed, most molecular clock disruptions influence multiple systems including locomotor activity and feeding patterns (Table 1). However, some specific deletions in certain tissues or brain areas that do not alter feeding and activity patterns do show changes in parameters important for defining metabolic syndrome. For instance, Bmal1 deletion either in hepatocytes, pancreas or myeloid cells does not alter feeding and activity patterns but significantly impairs glycaemia (Table 1). Similarly, although REV-ERBα has been shown to regulate Bmal1 expression directly, whole body Rev-erba KO mice display only a slightly shortened period [70] while these mice show profound dyslipidemia [49,68], disrupted gating of endotoxin-induced inflammation [67] and impaired mitochondrial biogenesis, leading to compromised exercise capacity [69]. Taken together, the studies reviewed herein raise intriguing questions concerning the impact of circadian misalignment and clock gene disruption on obesity and the development of adverse metabolic outcome. Nevertheless, these observations are largely based on animal studies, while knowledge in human circadian behavior and physiology remains limited. A central challenge will be to complete the understanding of human diurnal physiology. Within this context, new data collected in healthy human illustrate the temporal organization of the transcriptome and metabolome [117,118]. Moreover, another important aspect of this field is the intimate interconnection between nutritional status and circadian clock, bringing an additional layer of complexity to circadian homeostasis. Indeed, molecular clocks also respond to nutrient as well as metabolic transcription factors and transcriptional co-activators, constituting a reciprocal interconnection between timekeeping and metabolic systems [119]. A future goal will be to understand how macronutrient content of diet influences on circadian physiology and behavior. For example, HFD feeding disrupts the period of locomotor activity under free-running conditions, a core property of the clock [120]. Furthermore, HFD feeding alters clock gene expression in metabolic tissues [120,121], potentiating the adverse metabolic consequences induced by lipid overflow. Better knowledge in chronobiology may ultimately lead to improved therapeutics for MetS and CVD in human.

Disclosure of interest

J.B. has financial interest in and serves as advisor to Reset Therapeutics, Amylin Pharmaceuticals, and has been a paid consultant for Merck, Janssen Pharmaceuticals, Vanda Pharmaceuticals, Gerson Lehrman Group, and Matsutani America.

Acknowledgements

We thank members of the Bass, Takahashi, Turek and Allada laboratories for helpful discussions.

Funding: This work was supported by Alfediam (to E.M.), NIH (P01 AG011412 and R01HL097817-01 to J.B.), American Diabetes Association (to J.B.), Chicago Biomedical Consortium Searle Funds (to J.B.), Juvenile Diabetes Research Foundation (to J.B.), and the University of Chicago Diabetes Research and Training Center (P60 DK020595).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.12.005.

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