Cellular Physiology and Biochemistry

Cell Physiol Biochem 2022;56(S2):1-11
DOI: 10.33594/000000489
Published online: 15 January 2022
Accepted: 3 January 2022

Review

The Mechanisms and Physiological Consequences of Diurnal Hepatic Cell Size Fluctuations: A Brief Review

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Key Words
Liver • Hepatocytes • Circadian clock • Feeding • Cell size/volume • Osmotic cell regulation • Insulin/glucagon • mTOR

Abstract
Liver size in mammals fluctuates throughout the day and correlates with changes in hepatocyte size. However, the role of these daily changes in liver and hepatocyte size and the underlying molecular mechanisms remain largely unknown. In this review, we highlight the view that hepatocyte size, and thus, overall organ size, is subject to regulation by the circadian clock and feeding/fasting cycles. To that end, we provide an overview of the current literature dealing with this phenomenon and elaborate the role of feeding and nutrients in this process. We will discuss the role of hepatic protein content and synthesis, which are both subject to diurnal regulation, in daily hepatocyte and liver size fluctuations. Although there is evidence that changes in hepatocyte and liver size are associated with daily variations in macromolecule content, there is also evidence that these changes in size may be actively regulated by modifications of the cells' osmotic environment. Future research will need to examine the intriguing possibility that hepatocyte and liver size fluctuations may be required for normal liver function and to reveal the underlying molecular mechanisms behind this process.

Introduction

The circadian clock is an evolutionarily conserved, endogenous mechanism which allows organisms to anticipate the daily changes in their environment due to the light/dark cycles resulting from the Earth's rotation around its own axis. The circadian clock regulates many aspects of an organisms' behaviour such as feeding/fasting cycles and physiology. Mammalian circadian clocks are hierarchically organised with a central clock located in the hypothalamic suprachiasmatic nuclei (SCN) [1, 2] and peripheral clocks present in peripheral tissues such as the liver [3-6]. Similar to the circadian clock of SCN neurons, peripheral clocks are self-sustained and autonomous. However, to adjust to daily environmental changes and to ensure

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phase coherence between body clocks, peripheral clocks are synchronized by the SCN master clock [3] which is in turn synchronized by environmental light received by the retina [7, 8]. On a molecular level, circadian clocks consist of interconnected transcriptional and translational feedback loops that regulate rhythmic gene expression with a 24 h cycle. The core loop consists of the BMAL1 (or ARNTL) transcription factor that, once heterodimerized with CLOCK or NPAS2, binds to E-box like elements in the promoters of circadian clock target genes to induce their expression [9, 10]. This includes also *Period* (*Per*) and *Cryptochromes* (*Cry*) [9, 11], which after their translation and accumulation in the cytosol, translocate into the nucleus and inhibit BMAL1 transcription, resulting in the inhibition of BMAL1-driven circadian clock target genes [12-14]. For a more in-depth review of the circadian clock, see [15, 16].

Of particular note, the circadian clock plays a key role in regulating metabolism. Many metabolic processes that take place in the liver, including glucose, bile acid and lipid metabolism, as well as hepatic detoxification, are coordinated with feeding/fasting cycles and are subject to circadian clock regulation [17-19]. Furthermore, the liver is also a secretory organ that synthesizes and secretes most blood proteins such as albumin, coagulation factors, and complement proteins involved in the immune response. Interestingly, most of these proteins exhibit rhythmic levels in the blood of both rodents [20, 21] and human [22, 23]. However, the role of the circadian clock on the secretion of these proteins seems limited, with rather a critical role of feeding rhythms on the regulation of this secretion [24].

The genes and proteins involved in these processes are orchestrated by environmental cues via the SCN master clock and/or by the cell-autonomous peripheral liver clock itself [15, 25, 26]. Circadian regulation of liver function occurs on multiple regulatory levels of gene expression, including transcription [27-29], post-transcriptional regulation [30, 31], mRNA translation [32-34], post-translational regulation [35, 36], protein trafficking [37], and secretion [24]. Increasing evidence associates liver gene and protein expression with daily (or diurnal) fluctuations in liver size (Fig. 1). The exact role of this phenomenon is unknown but might be related to physiological organ functions. It thus might be of medical interest as it can serve as a readout for a normal and "healthy" organ status. For example, hepatocyte size fluctuations also correlate with liver portal blood pressure suggesting an impact of the volume of the hepatocyte compartment on the size of blood vessels [38, 39] (Fig. 1 and 2). Moreover, an increased liver/hepatocyte size and lower size fluctuations have been also associated with cirrhosis and chronic alcohol consumption [40, 41]. However, the factors and mechanisms contributing to liver size fluctuations remain to date poorly understood. That said, recent evidence suggests that daily fluctuations in liver size are regulated by the circadian clock and the associated feeding/fasting cycle. Here, we provide an overview of the current literature supporting this idea and summarize the body of work dealing with the potential underlying molecular mechanisms, including the role of hepatic macromolecule content and protein synthesis and changes in hepatocyte cell volume via osmotic regulation.

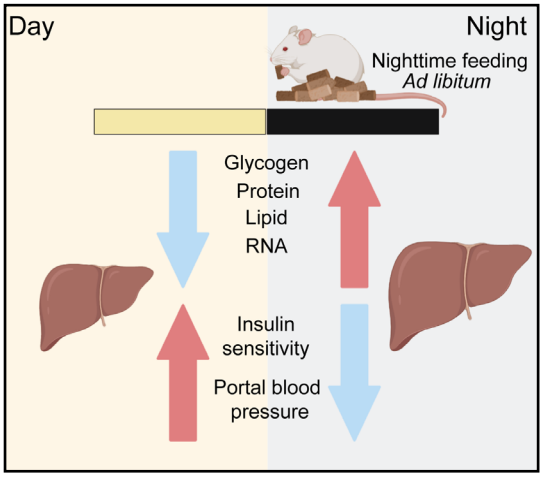

Fig. 1. The mouse liver shows diurnal fluctuations. Daily fluctuations in liver size correlate with macromolecules content (top: e.g., glycogen, protein, lipids, and RNA) and liver physiology (bottom) when animals are kept under an ad libitum or night restricted (=night-time) feeding regimen. Figure was created with BioRender.com.

Daily fluctuations in hepatocyte size are feeding dependent

Daily liver size fluctuations were first reported in birds, where it was found that liver weight is decreased during the night [42, 43]. Liver size fluctuations were later observed in humans, but the nature of the data (i.e., only a partial cycle from 8am to 8pm was measured and no control of food intake was done) did not allow a proper evaluation of the timing and the amplitude of these fluctuations [41, 44]. In mice, liver size fluctuates throughout the 24h cycle, with a maximum size at the night-day transition and a minimum size at the day-night transition. These changes in liver size are accompanied by diurnal size fluctuations of hepatocytes [37, 45] (Fig. 2), which are the main parenchymal cells of the liver. As hepatocytes constitute around 80% of liver mass [46], daily changes in hepatocyte size are likely the main contributors to fluctuations in liver size. Interestingly, hepatocyte size fluctuations are only detected in mice with a natural feeding/fasting cycle, when the timing of food consumption is in synchrony with their nocturnal activity pattern [47]. This means that only mice fed during the night (*i.e.,* under night-restricted/night-time feeding) or with an *ad libitum* access to food, under which mice mainly consume their food during the night phase [17, 48], show diurnal fluctuations in hepatocyte size [47]. Together with the fact that feeding and fasting and, thus, nutrient availability is a crucial factor for liver and hepatocyte size [49, 50], these observations point to feeding as a crucial factor in regulating hepatocyte size and liver size. In fact, a growing body of evidence suggests that the feeding/fasting cycle is an important driver of liver physiology by regulating hepatic gene transcription [51-55] and protein synthesis [32-34]. For example, a recent study investigating the role of feeding/fasting cycles on hepatic gene expression found that only 30% of rhythmic liver genes are directly driven by the molecular liver clock, yet more than 50% of rhythmic genes are dependent on systemic signals [29], which includes the feeding/fasting cycle [55]. Rhythms in food intake are dampened in animals with a disrupted molecular circadian clock [29, 53, 56-58]. It is therefore likely that decreased rhythmic mRNA expression and translation in circadian clock-disrupted animals is largely a result of the loss of a functional SCN master clock that controls the timing of feeding behaviour [59-61] rather than by a direct regulation of the liver clock.

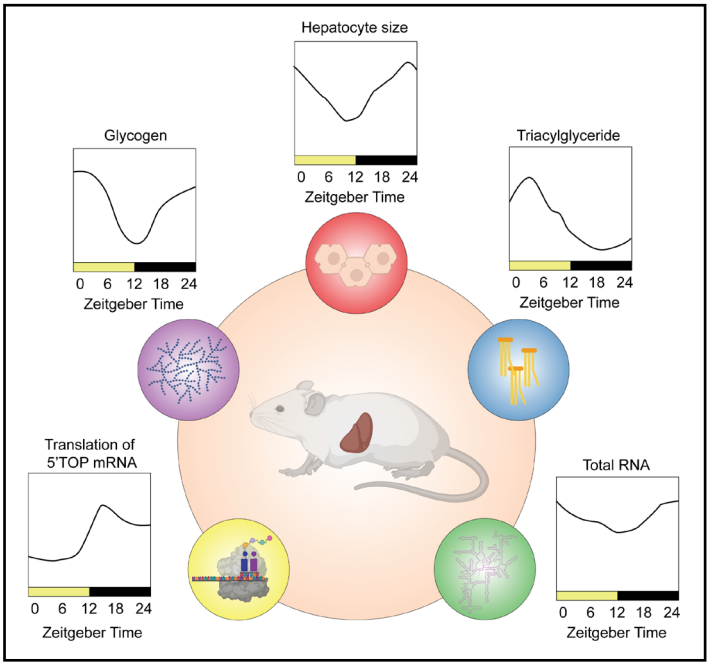

Fig. 2. The mouse liver is subject to daily fluctuations on many levels. These include the size of hepatocytes, the major parenchymal cell of the liver [37], and several hepatic macromolecules including triglycerides [109], glycogen [37], total RNA (a proxy for ribosomal RNA) [47], and translation of the mTOR-regulated 5'-TOP mRNA that encode for ribosomal proteins and translation elongation factors [32]. ZT, Zeitgeber time: the time lights were switched on (ZT0; yellow) or off (ZT12; black). Figure was created with BioRender.com.

Potential mechanisms for feeding dependent hepatocyte fluctuations

Though it is clear that the feeding/fasting cycle plays an important role in hepatocyte and liver size fluctuations, the underlying mechanisms have yet to be determined. One possibility discussed below is that hepatocyte and liver size changes may be a result of daily fluctuations in hepatic macromolecule content, but it is still unclear whether this goes beyond correlation.

The role of macromolecules and protein synthesis

In synchrony with liver size, lipid content (an integral part of the cell plasma membrane), glycogen (the storage form of glucose), ribosomal RNA, and proteins also fluctuate throughout the day [37, 43, 47] (Fig. 1 and 2). As proteins constitute most of the liver's dry mass, and protein synthesis that peak at night [34, 47], cellular fluctuation in protein content may mainly contribute to changes in liver size [47]. The number of ribosomes has been observed to follow a diurnal pattern similar to protein content [34, 47, 62], suggesting that the ribosome number is critical for translation efficiency and is rate limiting for hepatic protein synthesis [34, 47]. In fact, both ribosomal proteins and ribosomal RNAs show diurnal fluctuations in the liver through a mechanism involving their rhythmic synthesis [34, 47] and polyadenylation-dependent degradation [47]. The decrease in protein content during the day might be also a result of rhythmic protein degradation via autophagy, likely to compensate for the decrease in nutrient intake during the sleep/fasting period [63]. The recently described fasting-induced specific degradation of ribosomes via ribophagy might also play a role in the decreased protein content during the day [64]. Thus, ribosome synthesis/degradation might be a way to store an excess of food-derived amino acids and nucleotides during the night (murine activity phase) and use them during the day (murine resting phase) to maintain constant levels, in a similar fashion as glycogen synthesis and breakdown keeps blood glucose at constant level. In this context, fluctuations in hepatocyte size would be a concomitant feature that is driven by daily changes in hepatic protein synthesis and content. This would be in line with the concept that protein synthesis, a highly energy-dependent process, is actively restricted to times when enough energy and nutrients are available.

The role of osmotic cell regulation of hepatic cell volume

It is well-established that virtually all vertebrate cells have the capacity to actively undergo changes in cell volume through cell swelling (also called hydration) and shrinkage which is based on their ability to take up or release cellular ions and organic osmolytes. The dynamics of these processes have been described to occur on a time scale of few minutes. However, it is tempting to speculate that at least some of the suggested factors implicated in osmotic cell regulation and their linked functions [65, 66] might play a role in the diurnal regulation of cell and liver size. For example, cytoskeletal elements involved in the organization of the microtubular structure or the actin cytoskeleton, characterized by the ratio between F and G actin, are remodelled by cell volume changes [67, 68] and contribute to cell swelling-dependent proteolysis [69, 70]. Accordingly, they also exhibit diurnal dynamics in mouse liver [45], suggesting that they may be involved in this process. In fact, there is some evidence that daily fluctuations in hepatocyte cell volume may actually drive changes in macromolecule content rather than the other way around. Although the precise molecular mechanisms are still poorly understood, changes in cell volume are known to play a crucial role in cell physiology, modulating both gene expression and metabolism [65, 66] including the synthesis and degradation of glycogens [71-73] and proteins [74-76]. More research is needed to answer the question of how changes in cell volume and macromolecule content is related to diurnal regulation of hepatocyte size and liver size.

Insulin/glucagon and mTOR signalling as potential mediators

Insulin/glucagon signalling is an important feeding-dependent regulator of metabolism [77], and previous research suggests that it is important for liver size fluctuations. The liver-specific loss of the insulin receptor is known to impact liver size [78, 79], and the rhythmic secretion of insulin and glucagon is subject to circadian clock regulation [80-82]. Moreover, this pathway has been identified as a crucial regulator of hepatic cell volume and linked functions. For example, insulin stimulates the cellular retention of K^+ and thus allows hepatocyte swelling though an influx of water which mediates the inhibition of proteolysis and glycogen synthesis [83, 84], while glucagon counters the effects of insulin [84, 85]. In turn, fluctuations in liver size also influences the liver's insulin response, as insulin sensitivity is time-of-day and circadian clock-dependent, and maximum insulin actions occur when the liver has reached its smallest size [86, 87]. Interestingly, the inactivation of the 3-phosphoinositide-dependent protein kinase-1 (PDK1) that is involved in the regulation of ion transport during hepatocyte shrinkage [88, 89] also results in an increase in insulin sensitivity [90]. Conversely, inactivation of the serum- and glucocorticoid-regulated protein kinase 1 (SGK1) is involved in cell swelling [66] and is associated with insulin resistance [91]. Together, these results suggest that insulin plays an important role in the regulation of liver cell size which in turn impacts insulin sensitivity.

In addition to insulin/glucagon signalling, the mTOR (mechanistic Target of Rapamycin) signalling pathway has also been implicated as a regulator of hepatic cell volume and linked functions [92, 93]. It thus might be another important driver of daily liver size fluctuations. Activation of the mTOR signalling pathway, through the activity of complex 1 (mTORC1) and 2 (mTORC2), is a well-known nutrient responsive regulator that plays a crucial role in eukaryotic cell growth, metabolism, and mRNA translation/protein synthesis [94]. In line with mTOR's role in these processes, an inhibition or loss of mTOR factors reduces liver size in mice, whereas its activation leads to an increased liver size [79, 95, 96]. Notably, the activation of the mTOR signalling pathway is subject to circadian clock regulation [34, 35, 97, 98] and is involved in the rhythmic regulation of the translation of ribosomal proteins and translation regulation factors [32]. In this way, the mTOR signalling pathway drives rhythmic ribosome biogenesis and protein synthesis [34]. Nevertheless, the interconnection between the circadian clock and the mTOR pathway is poorly understood and further research is needed. Previous work has shown that BMAL1 is phosphorylated by the mTOR-effector kinase S6K1, leading to the regulation of mRNA translation by directly interacting with the translational machinery [99]. In line with this study, the negative regulator of BMAL1 activity, PER2, reportedly modulates mTORC1 activity in response to fasting in cell culture studies and thus could regulate BMAL1-induced protein translation [100]. Although the idea that the circadian clock can directly impact protein translation via the core clock members BMAL1 [99] and PER2 [100] is appealing, some discrepancies need to be considered. First, most genes (approximately 70%) that are rhythmically translated in mouse liver rely on rhythmic mRNA levels. The rhythmic translation of these genes is a result of a rhythmic transcription rather than an active rhythmic regulation of translation [32, 34]. Second, investigations in *Bmal1* knockout mice fail to confirm a predominant role of BMAL1 in rhythmic translation in the liver. Indeed, relative translation efficiency is globally conserved, and only a minor fraction of mRNAs (with the exception of mRNA encoding for ribosomal proteins) are differentially translated in the liver of *Bmal1* knockout mice compared with their wild-type littermates [32]. Thus, the modulation of the mTOR pathway by the circadian clock may instead occur indirectly through the regulation of the feeding/fasting cycle [32, 51], rRNA transcription and stability [34, 47], and protein transport into the nucleus [37].

Conclusion

As discussed here, liver size fluctuations correlate with daily changes in nutrient uptake, storage, and metabolism. Liver size increases with nutrient intake and storage during the active/feeding period and decreases when stored nutrients are broken down during the sleep/fasting period (Fig. 1 and 2). However, these size fluctuations appear to be a more complex process rather than simply a passive "dilatation" of the liver in response to macromolecule synthesis and storage; additional mechanisms of cell volume regulation are likely involved as well. These mechanisms may potentially even be actively driving liver size fluctuations. However, many questions remain and further research will be required to answer these complex questions and to obtain a better understanding of the underlying mechanisms.

Although this review article has focused on the liver, it is possible that the mechanisms discussed here might also be relevant for other organs: daily fluctuations in size or volume have also been reported in the brain [101-103], eye [104, 105], spleen [106], pancreatic β-cells [107], and epithelial cells of the intestine [108]. With the improvement of *in vivo* imaging techniques, it would be interesting to measure daily changes in tissues' size in both healthy and pathological conditions, or in conditions of perturbed circadian rhythms as during shift work. This would help to understand their physiological functions and define potential new biological markers of multiple disease states.

Acknowledgements

B.D.W is supported by an UQ Early Career Researcher Grant (UQECR2058233) and F.G. receives support from the Institute for Molecular Bioscience, The University of Queensland.

Disclosure Statement

The authors declare they have no conflict of interests.

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