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Molekulární mechanismus synchronizace cirkadiánních hodin režimem příjmu potravy
Molecular mechanisms of circadian clock entrainment by daily regime in food intake

Bakalářská práce

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Poděkování

Chtěl bych tímto poděkovat své školitelce, paní PharmDr. Aleně Sumové, DSc., za trpělivost a ochotu při zpracovávání této bakalářské práce.

Prohlášení

Prohlašuji, že jsem závěrečnou práci zpracoval samostatně a že jsem uvedl všechny použité informační zdroje a literaturu. Tato práce ani její podstatná část nebyla předložena k získání jiného nebo stejného akademického titulu.

V Praze 21. 8. 2017

Mgr. Jiří Kapoun

List of abbreviations

AMP	adenosine monophosphate
AMPK	AMP-activated protein kinase
ATP	adenosine triphosphate
BMAL1	brain and muscle arnt-like protein 1
cAMP	cyclic adenosine monophosphate
CCG	clock controlled gene
CKIδ	casein kinase delta
CKIε	casein kinase epsilon
CLOCK	circadian locomotor output cycles kaput
CO	carbon monooxide
CBP	CREB-binding protein
CR	calorie restriction
CREB	cAMP response element-binding protein
CRY	cryptochrome
DHA	docosahexaenoic acid
DRN	dorsal raphe nucleus
EPA	eicosapentaenoic acid
EZH2	enhancer of zeste homolog 2
FA	fatty acid
GABA	gamma-aminobutyric acid
GR	glucocorticoid receptor
HAT	histone acetyltransferase
HDAC	histone deacetyltransferase
IF	intermittent fasting
IGL	intergeniculate leaflets
KLF10	Krüppel-like factor 10
LBD	ligand binding domain
LKB1	liver kinase B1
MAPK	mitogen-activated protein kinase
MLL1	mixed lineage leukemia 1
MRN	median raphe nucleus
NAD^+	nicotinamide adenine dinucleotide (oxidized)
NADH	nicotineamid adenine dinucleotide (reduced)
NAMPT	nicotineamid phosphoribosyletransferase
NCoR-HDAC3	nuclear repressor coreceptor-histone deacetylase 3
NMN	nicotinamide mononucleotide

NMNAT	nicotineamid mononucleotide adenyltransferase
NO	nitric oxide
NPAS2	neuronal PAS domain protein 2
NPY	neuropeptide Y
NR	nuclear receptor
PAI-1	plasminogen activator inhibitor 1
PCAF	p300/CBP-associated factor
PEPCK	phosphoenolpyruvate carboxykinase
PER	period
PGC-1α	PPARγ coactivator-1α
PK2	prokineticin 2
PPAR	peroxisome proliferator-activated receptor
qPCR	quantitative polymerase chain reaction
RF	restricted feeding
RHT	retinohypothalamic tract
RORα	RAR-related orphan receptor alpha
RRE	REV-ERB/ROR response element
SCN	suprachiasmatic nuclei
SIRT1	silent information regulator T1
SNP	single nucleotide polymorphism
TIEG1	TGFbeta inducible early gene-1
TIM	timeless
TNFα	tumor necrosis factor alpha
VDUP1	vitamin D3 upregulated protein 1

Abstract and keywords

Circadian clocks form an endogenous time-keeping system present in most organisms, synchronizing physiological and behavioural processes with perodically changing environmental conditions. The system comprises of the master clock in the suprachiasmatic nuclei of the hypothalamus and numerous subsidiary clocks in peripheral tissues. Its molecular design is constituted by the clock genes, which are rhythmically expressed, form a series of transcriptional/translational feedback loops and influence the expression of various other genes involved in metabolic pathways. The peripheral clocks are dependent on the master clock, although they can be entrained with external cues like food intake timing and diet composition. This desynchronization leads to the distruption of clock gene oscillation, which can potentially have serious impact on metabolic processes and increase the risk of metabolic disorders.

The aim of this thesis is to summarize current knowledge on the relationship of molecular chronobiology and nutrition with a focus on the molecular mechanisms through which can food, especially its intake timing and composition, influence the crosstalk between clock gene expression and cellular metabolism. The thesis also emphasises the potential effect of circadian clock disruption on the risk of metabolic disease development.

Keywords: circadian clock, food intake, entrainment

Abstrakt a klíčová slova

Cirkadiánní hodiny jsou vnitřním časoměrným systémem přítomným u většiny organismů, jenž synchronizuje fyziologické a behaviorální procesy s periodicky se měnícími vnějšími podmínkami. Skládají se z centrálních hodin v suprachiasmatických jádrech hypothalamu a řady dalších hodin v periferních tkáních. Jejich molekulární podstatu tvoří hodinové geny, které jsou rytmicky exprimovány, jsou součástí série transkripčně-translačních zpětnovazebných smyček a ovlivňují expresi různých jiných genů s funkcemi v metabolických drahách. Periferní hodiny jsou závislé na centrálních hodinách, ovšem mohou být synchronizovány nezávisle na nich vnějšími podněty, jako je načasování příjmu potravy a složení stravy. Tato desynchronizace vede k narušení oscilace hodinových genů, které může mít vážný dopad na metabolické procesy a může zvyšovat riziko metabolické poruchy.

Cílem této práce je shrnout dosavadní výzkum zabývající se vztahem molekulární chronobiologie a výživy se zaměřením na molekulární mechanismy, skrze které může potrava, zejména načasování jejího příjmu a její složení, ovlivnit vzájemnou komunikaci mezi expresí hodinových genů a buněčným metabolismem. Práce též vyzdvihuje možný dopad narušení cirkadiánních hodin na riziko vzniku metabolického onemocnění.

Klíčová slova: cirkadiánní hodiny, příjem potravy, synchronizace

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Introduction

Circadian clock, an inherent trait of most living organisms, represents an evolutionary adaptation to constantly fluctuating environmental conditions including primarily day and night cycles, but also periods of feeding and fasting. An internal clockwork system allows organisms to foresee such transitions and alter various biological processes in accordance with them. Among the most essential targets of circadian regulation are metabolic pathways and endocrine functions of peripheral tissues. The heart of the circadian clock at a molecular level consists of an intricate series of transcriptional/translational feedback loops that drive rhythmical expression on several so-called core clock genes in a circadian manner. Protein products of these clock genes afterwards work as transcription regulators for many other genes involved in numerous physiological processes. Circadian clock is constituted by a master clock in the suprachiasmatic nuclei of the hypothalamus and peripheral clocks present in various types of body tissues. The proper overall function of an organism depends on the synchrony between the master clock and peripheral clocks.

The molecular mechanisms of peripheral circadian clocks in mammals can be entrained by external cues, which override its synchronization with the master clock and alter the expression of clock genes therein. Food intake timing, diet composition and specific nutrients are all among these environmental signals capable of circadian clock entrainment. This feeding-driven entrainment of the circadian molecular clockwork can significantly impact enzyme function within metabolic pathways and even hormone secretion, eventually leading up to an increased risk of a metabolic disorder.

This thesis aims to present a compilation of existing research on the topic of molecular chronobiology and chrononutrition. The first chapter will provide an introduction to the subject of mammalian chronobiology, defining the integral parts of the circadian clock and mechanisms operating therein. The second chapter will delve deeper into the problematics of the communication between nutrition, cellular metabolic state and circadian clock on the molecular level by characterizing the possible means of feeding to influence the functions of cellular enzymes and nuclear receptors. The third chapter will describe the importance of food and feeding-related cues for the circadian clockwork. The last chapter will connect the disruptions of the circadian system with metabolic diseases such as obesity and type 2 diabetes.

1. Crucial elements and mechanisms of circadian clock entrainment

The following chapter aims to set a conceptual basis for the rest of the thesis by introducing and describing the mammalian circadian clock system – suprachiasmatic nuclei (SCN) of the anterior hypothalamus as the biological master clock, oscillators in peripheral tissues as subsidiary clocks and their relation to SCN and basic molecular mechanisms of circadian clock entrainment including transcriptional elements involved therein.

1.1 Suprachiasmatic nuclei as the master clock

The suprachiasmatic region of the anterior hypothalamus had been identified as the chief cause of mammalian biological rhythms through experiments conducted on rodents with the conclusion that specific bilateral lesions of the SCN led to the disruption of circadian rhythms in adrenal corticosterone production (Moore and Eichler, 1972), and in drinking behaviour and locomotory activity (Stephan and Zucker, 1972). This has been supported by following research proving that neural transplantation of SCN tissue from hamsters carrying certain clock gene mutations into wild-type hamsters with SCN lesions managed to transfer the mutant phenotype to the recieving animal and restore rhythmic activity (Ralph et al., 1990). A similar experiment has been conducted on mice revealing that transplantation of fetal SCN tissue re-estabilished rhythmic activity in specific circadian-genes-knockout specimens (Sujino et al., 2003).

Suprachiasmatic nuclei are paired, bilaterally arranged neural structures adjoining the optic chiasm and are of relatively small dimensions in comparison with other nuclei of the hypothalamus (Ibata et al., 1999). SCN function as a central circadian pacemaker and relay external photic information to specific body tissues. They recieve environmental information mainly via the retinohypothalamic tract (RHT) comprised of non-rod, non-cone photoreceptors (Freedman et al., 1999) – photosensitive retinal ganglion cells capable of intrinsic phototransduction (Berson et al., 2002). There is also an alternative pathway, which redirects the RHT to thalamic intergeniculate leaflets (IGL) and through the geniculohypothalamic tract (GHT), utilizing neuropeptide Y (NPY) as a mediator, to the SCN (Yannielli and Harrington, 2001; Freeman et al., 2004). A third pathway conveys non-photic input to the SCN from serotonergic median raphe nucleus (MRN) and dorsal raphe nucleus (DRN) neurons in the brain stem (Meyer-Bernstein and Morin, 1996). The pathways leading efferently from the SCN transduceing recieved signals to both intra-hypothalamic and extra-hypothalamic structures project particularly into the subparaventricular zone of the hypothalamus, the preoptic area, the anteroventral periventricular nucleus and the anterodorsal preoptic nucleus (Morin et al., 1994). The prokineticin 2 (PK2) has been discovered as one of the principal output molecules, which at the same time is a major clock-controlled factor (Cheng et al., 2005). Other neurochemical transmitters in the SCN include gamma-aminobutyric acid (GABA), glutamate (Hermes et al., 1996), arginine vassopresin and vasoactive intestinal peptide (Abrahamson and Moore, 2001).

As mentioned above, day-night (or light-dark) cycles are the principal and the most potent *zeitgeber* („time giver“) entraining mammalian circadian rhythms (Pittendrigh, 1981), though they are not the only one – cycles of high and low ambient temperature have been proven to entrain locomotor activity rhythms in certain rodents (Rajaratnam and Redman, 1998) and the potential of food availability cycles („restricted feeding“) to reset the circadian machinery in mice has also been discovered (Abe et al., 2007).

1.2 Molecular mechanisms of circadian oscillation

The intracellular circadian machinery of the SCN is comprised of a complex of both positive and negative transcriptional/translational feedback loops (Shearman et al., 2000) as shown in the diagram below (Fig. 1).

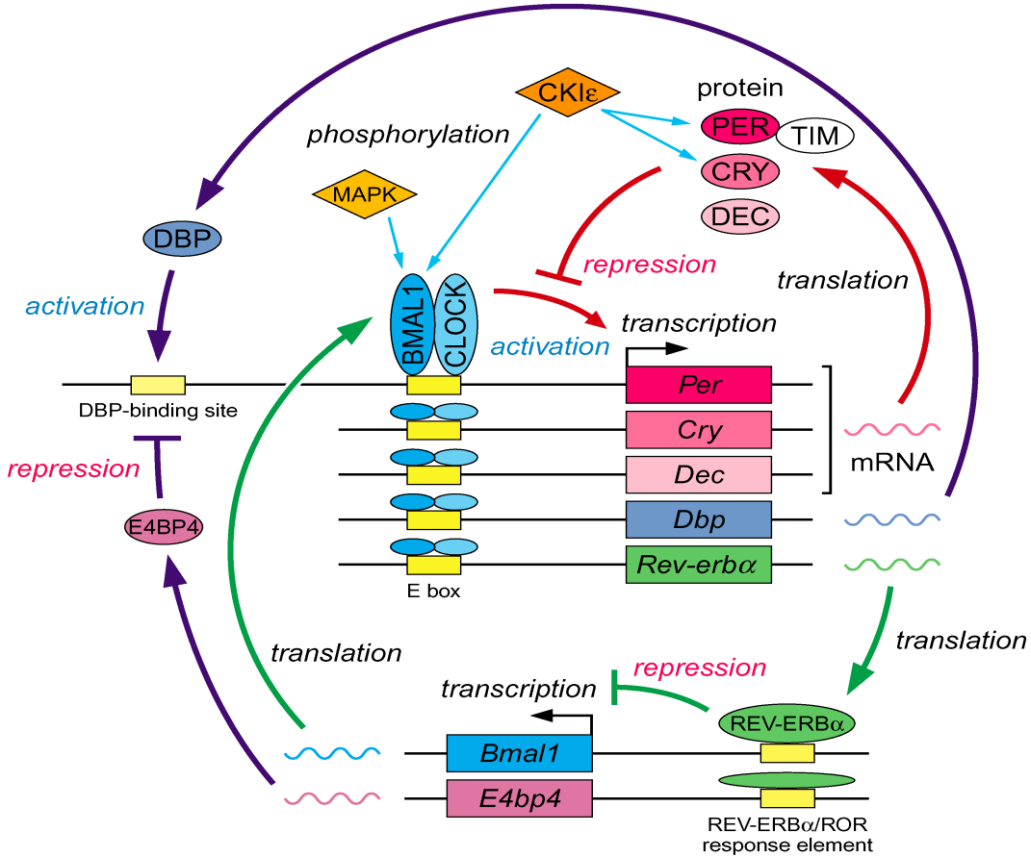

Fig. 1: A general scheme of the molecular clockwork system including crucial feedback loops (reviewed in Hirota and Fukada, 2004).

In the centre of the core clock mechanism, there can be found two fundamental transcription regulators – BMAL1 (brain and muscle Arnt-like protein 1) and CLOCK (circadian locomotor output cycles kaput) forming a heterodimetric regulatory element which enters the nucleus, binds to the E box sequence in the promoter region of other clock genes, namely *Per1, Per2* (*Period*), *Cry1 and Cry2* (*Cryptochrome*). After the binding it activates their transcription and, therefore, CLOCK:BMAL1 acts

as a positive element in the loop (Honma et al., 1998). Both BMAL1 and CLOCK proteins inherently carry a specific conserved sequence called the PAS (PER-ARNT-SIM) domain and a basic helix-loop-helix structural motif which are responsible for protein-protein interactions and DNA binding (Ikeda and Nomura, 1997; Gekakis et al., 1998). In turn, after the *Per* and *Cry* transcripts are translated in the cytoplasm, their proteins form a heterodimeric structure which enters the nucleus and inhibits the CLOCK:BMAL1-dependent transcriptional activation – the PER:CRY complex therefore acts as a negative element in the loop (Shearman et al., 1997; Kume et al., 1999).

The negative arm of the feedback loop includes other regulatory elements, namely the mammalian homologue of *Tim (Timeless)* found first in the *Drosophila* fruit fly. The TIM element interacts with PER2 forming a heterodimer capable of *Clock/Bmal1* transcription inhibition (Barnes et al., 2003). Another part of the loop is represented by translational products of the *Dec* gene with a function similiar to that of *Tim* (Honma et al., 2002). Later, it has been found that *Tim* is not essential for the core clock mechanisms in mammals and, therefore, is not listed as a clock gene (Engelen et al., 2013); it is however important for embryonic development (Gotter et al., 2000).

Among the most important clock genes is *Rev-erbα*, whose expression is controlled by the CLOCK:BMAL1 transcription factor. Its translational product, REV-ERBα, binds to the REV-ERB/ROR response element (RRE) in *Bmal1* promoter and inhibits the transcription of *Bmal1* (Preitner et al., 2002). The translational product of another clock gene, *Rorα* (RAR-related orphan receptor alpha), also binds to the RRE element of *Bmal1* promoter and activates its transcription. REV-ERBα and RORα have been found to compete for binding to *Bmal1* promoter, thus driving the rhythmic expression of *Bmal1* (Sato et al., 2004).

Translational products of clock genes are subject to post-translational modifications, particularly phosphorylation by mammalian casein kinase I epsilon (CKI_{ε}), which phosphorylates PER elements, positively influences their turnover and therefore regulates *Clock/Bmal1* expression (Lee et al., 2001). Aside from CKI_{ε}, casein kinase I delta (CKI_{δ}) with similiar properties and functions has also been found in mammals (Akashi et al., 2002). Other mechanisms of clock regulation include phosphorylation via mitogen-activated protein kinase (MAPK), which associates with BMAL1 and inhibits CLOCK:BMAL1-induced transcription of clock genes (Sanada et al., 2002), and adenosine monophosphate-activated protein kinase (AMPK), which targets the CRY1 element, causing its destabilization and subsequent degradation (Lamia et al., 2009).

Genome-wide transcriptome profiling research managed to prove the existence of a close relationship between circadian clock mechanisms and metabolism – around 10 percent of mammalian transcription products of the so called clock-controlled genes (CCGs) in peripheral tissues, mainly in the liver, follow daily cycles in accumulation. Many of these transcripts encode various enzymes and other regulatory molecules of carbohydrate and lipid metabolism (Akhtar et al., 2002; Duffield et al.,

2002). To elucidate this genetic and physiological link, experiments on mice have been conducted revealing that homozygous *Clock* mutants, that possess singificantly attenuated diurnal feeding rhythms, are often obese and prone to metabolic disorders such as hyperlipidemia and hyperglycemia (Turek et al., 2005).

1.3 Circadian clocks in peripheral tissues

Mammalian biological circadian machinery comprises not only of the SCN as the master clock, but also of peripheral clocks located in specific body tissues, which are to a certain extent controlled and synchronized by the master clock. Experiments conducted on rats proved that peripheral clocks exhibit identical molecular mechanisms as the master clock (Yagita et al., 2001) and oscillate with a distinct phase difference from the SCN ranging from 7 to 11 hours (Yamazaki et al., 2000). Peripheral oscillators have been found in many neuronal and non-neuronal body tissues, namely in the liver, lungs, kidneys, pancreas, skeletal muscles and others organs (Balsalobre et al., 1998). Experiments with SCN lesions and consecutive transplanations in Syrian hamsters have found that master clock destruction fully disrupted peripheral circadian rhythms, but successive SCN tissue transplantation reinstated them only in some peripheral organs, not all – rhythms were successfully restored in kidneys and liver, unsuccessfully in heart, spleen and adrenal medulla (Guo et al., 2006).

The SCN generally tends to set up phase coherence by entraining the phases of peripheral clocks through several major pathways. The more direct route employs various neuronal and humoral signals, for example gluccocorticoid hormones, whose plasmatic levels oscillate significantly during the day in accordance with hypothalamic-pituitary-adrenal axis activity (Oster et al., 2006). Another pathway is constituted by the autonomic nervous system (Cailotto et al., 2009). The undirect route includes *zeitgebers* such as environmental and endogenous temperature cycles (Brown et al., 2002) and most importantly temporal feeding restrictions pursuant to specific light-dark conditions (Damiola, 2000) – this phenomenon will be discussed in chapter 3.

1.3.1 Circadian clock in the liver

High-density microarray studies on mice have proven that some of the major metabolic processes in liver cells are under circadian control and rate-limiting steps of these pathways are regulated by clockwork mechanisms (Panda et al., 2002). According to a more recent proteomic research, around 6 percent of liver proteins are subject to circadian cycling and post-transcriptional mechanisms are crucial in setting up and tuning the phase of metabolic rhythms, likely more important than transcription regulation facilitated by clock gene products (Robles et al., 2014). A number of fundamental rate-limiting enzymes of glucose and lipid metabolisms, for example of the glycerol 3-phosphate pathway, are synthesized in a circadian manner, influencing the level of triglyceride accumulation (Adamovich et al., 2014). The role of peripheral liver clock is summarized in the schematic below (Fig. 2).

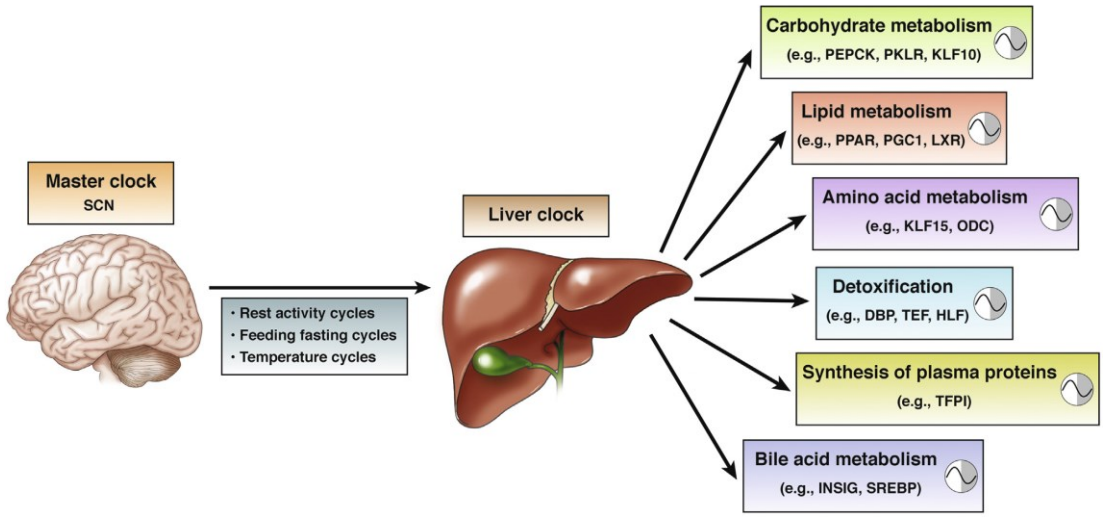

Fig. 2: A brief overview of the effect of circadian clocks on liver physiology (reviewed in Reinke and Asher, 2016).

Along with pancreas, skeletal muscles and brain, liver plays a critical role in glucose homeostasis maintenance by buffering rhythmic fluctuations of glycemia caused by brain-driven fasting-feeding cycles. Experiments conducted on mice revealed that *Bmal1* knockout mice exhibited exaggerated fluctuations in blood glucose levels immediately after its absorption in hepatocytes (Lamia et al., 2008).

Concerning gluconeogenesis, *Bmal1* deletion leads to its complete abortion, whereas *Clock* mutation leads to its decline (Rudic et al., 2004). Another mechanism how circadian clock controls hepatic gluconeogenesis is through the activity of CRY1 and CRY2, which interact with G-protein coupled receptors, blocking the accumulation of cAMP and stimulating the expression of gluconeogenic genes regulated by CREB (cAMP response element-binding protein) (Zhang et al., 2010). Alternatively, the two cryptochromes are capable of repression of transcription of phosphoenolpyruvate carboxykinase (PEPCK), an enzyme of gluconeogenesis – on the molecular

level, cryptochromes bind to the promoter region of PEPCK 1. *Cry1*/*Cry2* knockout mice exhibited glucose intolerance and high levels of blood corticosteron (Lamia et al., 2011).

Another link between molecular circadian mechanism and liver energy metabolism is constituted by the activity of Krüppel-like factor 10 (KLF10), whose expression is activated through CLOCK:BMAL1-E box binding and which in turn acts as a transcriptional regulatory factor for various enzymes involved in gluconeogenesis, glycolysis and lipogenesis. Experiments on mice have revealed that female *Klf10* mutants exhibit higher triglyceride levels than mutant males. On the other hand, male *Klf10* mutants show signs of hyperglycemia in the fasting period, whereas female mutants do not (Guillaumond et al., 2010).

Regarding the influence of circadian rhythms on lipid metabolism, recent lipidomic research managed to prove that approximately 17 percent of hepatic lipids are subject to diurnal oscillations in both *Clock*-null and wild-type mice, although the phases and molecular composition of the fractions were different (Adamovich et al., 2014). According to metabolome examinations, *Clock*-mutated specimens exhibited disrupted expression of certain lipid metabolism genes and therefore disorganized accumulation of respective metabolites (Eckel-Mahan et al., 2012).

1.3.2 Circadian clock in the pancreas

Another key player in mammalian metabolic regulation, particularly in glucose homeostasis management, is the pancreas, which has been proven, much like the liver, to possess an intrisic circadian clock machinery. The circadian clock is located in beta cells of pancreatic isles as well as in the exocrine part. Mutations of clock genes *Clock, Bmal1* and *Per1* in mice led to glucose intolerance, deficient synthesis of insulin (Sadacca et al., 2011) and progressive impairment of islet growth (Marcheva et al., 2010).

Experiments conducted on human pancreatic cells proved that isolated islets contained inherent autonomous circadian clocks. According to qPCR (quantitative polymerase chain reaction) results, islet clock genes *Bmal1, Cry1, Rev-erbα, Per1, Per2* and *Per3* exhibited rhythmic circadian oscillations and the phase of the expression of *Bmal1* and *Cry1* transcripts was reversed in comparison with the rest of the aforementioned genes (Pulimeno et al., 2013).

One of the critical clock genes, *Rev-erbα*, has been found to play a major role in both insulin and glucagon secretion. Downregulation of *Rev-erbα* in pancreatic β cells has been found to impair glucose-stimulated insulin secretion by reducing the expression of specific exocytosis genes such as *Vamp3* and *Munc18* (Vieira et al., 2012). In pancreatic α cells, which are responsible for glucose-stimulated glucagon secretion, *Rev-erbα* influences their activity via aforementioned exocytosis regulation and a specific AMPK/NAMPT/SIRT1 pathway (Vieira et al., 2013).

1.3.3 Circadian clock in the adipose tissue

Adipose tissue consists of adipocytes, which have also been found to possess a wide array of active genes through expression profiling experiments (Maeda et al., 1997). Translational products of these genes are the so called adipocytokines – specific secretory physiologically active molecules including leptin, TNFα (tumor necrosis factor α) and adiponectin playing various roles in mammalian metabolic cycles (Funahashi et al., 1999). Both leptin and adiponectin are expressed in a circadian manner (Ahrén, 2000; Calvani et al., 2004).

Leptin, the product of the *Ob* (*Obese*) gene, is a peptide hormone with a satiety-sensor function which regulates feeding patterns via hypothalamic receptors (NPY synthesis and release inhibition) (Stephens et al., 1995). Leptin serum levels have been proven to be in correlation with general adiposity (body fat percentage) in mammals with the concentration being approximately quadruple in obese specimens (Considine et al., 1996). Experiments showed that adipocytokine levels in *Bmal1*-null mice were generally higher than in wild-type mice and these mutant mice had also higher percentage of body fat, despite weighing less (Kennaway et al., 2013).

Circadian machinery influences not only adipocytokine synthesis, but adipogenesis as well – BMAL1 plays an important role in the phase of adipocyte differentiation, when its levels are significantly increased, and is required for proper adipogenesis. *Bmal1* knockout severely impaires lipid droplet accumulation in maturing 3T3-L1 cells (Shimba et al., 2005). On the other hand, *Bmal1* deficient mice tend to show signs of obesity and increased adiposity in general due to higher leptin levels and different feeding patterns (Lamia et al., 2008). PPARγ (peroxisome proliferator-activated receptor γ) is another regulator of adipocyte differentiation capable of stimulating fibroblast to turn into adipocytes (Tontonoz et al., 1994). The activity of PPARγ is connected to a number of specific coregulators, most notably PPARγ coactivator-1α (PGC-1α), working as switches capable of both positive and negative target gene transcription regulation (Feige and Auwerx, 2007). These coregulators are probable targets of several circadian transcription regulatory molecules and therefore connect circadian clocks to adipose tissue differentiation (Koike et al., 2012).

2. Genetic links between circadian and metabolic systems

This chapter will shift the focus from the fundamentals of mammalian circadian clock system towards more specific molecular mechanisms through which cellular metabolism communicates with the circadian clock. The following diagram lays out the most important pathways for metabolic cues to influence circadian rhythms within the cell (Fig. 3).

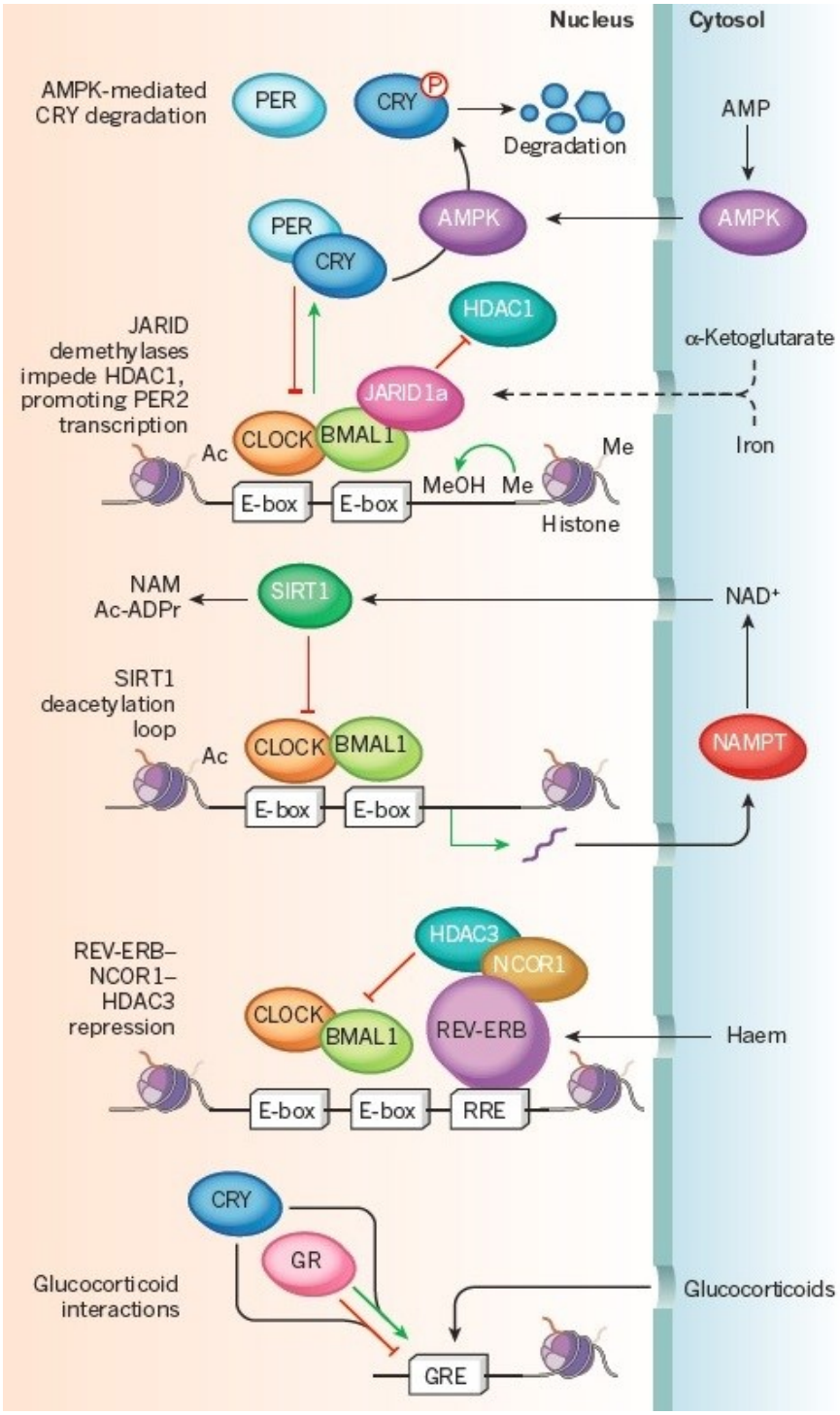

Fig. 3 – An overview of genomic and epigenetic links between the cellular metabolic state and circadian machinery within the cell core (reviewed in Bass, 2012).

2.1 The role of AMPK in CRY and PER degradation

AMPK, or AMP-activated protein kinase, is a mammalian enzyme allosterically activated by AMP (adenosine monophosphate), capable of AMP-dependent protein phosphorylation and their subsequent inactivation. It is sensitive to intracellular AMP/ATP ratio and is activated during low-energy states by AMP concentration increase and ATP concentration decrease (Yeh et al., 1980). Structurally, it is a heterotrimeric complex comprising of α, β and γ subunits (each a product of one of up to three genes – *α1*, *α2*; *β1*, *β2*; *γ1*, *γ2*, *γ3*), where the alpha subunit has a catalytic function, beta and gamma are noncatalytic subunits (Gao et al., 1995; Stapleton et al., 1994).

The interaction of AMPK and the circadian clock is illustrated in the schematic below (Fig 4).

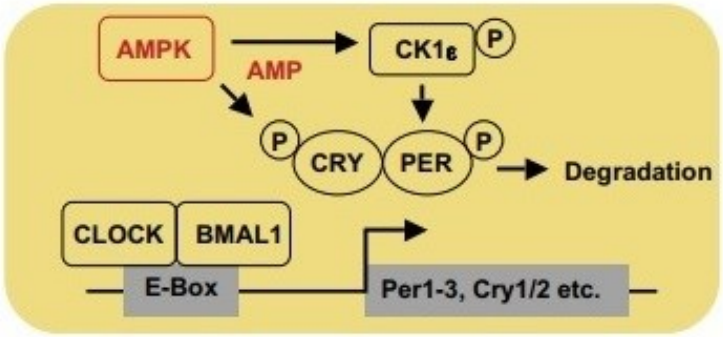

Fig. 4 – A diagram symbolizing the protein kinase effect of AMPK on clock gene products (reviewed in Jordan and Lamia, 2013).

AMPK is a nutrient-responsive protein kinase playing a role in the destabilization and degradation of CRY clock element via its phosphorylation – it has been discovered that AMPK directly phosphorylates serine 71 and serine 280 in CRY, marking it for consequent degradation mediated by FBXL3, an F-box protein (Ho et al., 2006). Concerning the link between AMPK, CRY and nutrition, this means that lowered glucose intake increases the activity of AMPK, weakens the stability of CRY and reduces its endogenous levels, leading to a phase shift of circadian clock in mouse fibroblast and liver (Lamia et al., 2009). In skeletal muscle, AMPK complexes containing the γ_3 subunit play a specific role in circadian clock synchronization (Vieira et al., 2008).

Moreover, AMPK has also been found to possess the capacity to phosphorylate casein kinase I epsilon (CKI_ε) at serine 389, enhancing its activity in peripheral tissues. CKI_ε is responsible for targeted PER phosphorylation, which leads to its destabilization and proteasomal degradation (Um et al., 2007).

AMPK is linked to another crucial enzyme of the nutrition-responsive clockwork system – SIRT1 (silent information regulator T1), which will be more closely described in chapter 2.2. Activation of AMPK is followed by NAD^+/NADH ratio increase via enhanced mitochondrial fatty acid β-oxidation, subsequently leading to an increase in SIRT1 activity, which is a NAD^+-sensitive type III deacetylase (Cantó et al., 2009). AMPK is in turn positively regulated by SIRT1 via LKB1 (liver kinase B1, one of

the most prominent AMPK kinases) acetylation impairment, which leads to an increase of its kinase activity and AMPK-activation ability (Lan et al., 2008).

2.2 Sirtuins as NAD^+-sensitive protein deacetylases

Mammalian histone deacetyltransferases (HDAC) have been separated into several families, where classes I, II and IV are represented by Rpd3/Hda1 HDACs and class III is comprised of sirtuins (Yang and Seto, 2008). Sirtuins are NAD^+-dependent protein deacetylases regulating not only mitochondrial fatty acid metabolism (Lombard et al., 2007; Hirschey et al., 2010), but also circadian gene expression pursuant to cellular NAD^+ levels (Imai and Armstrong, 2000).

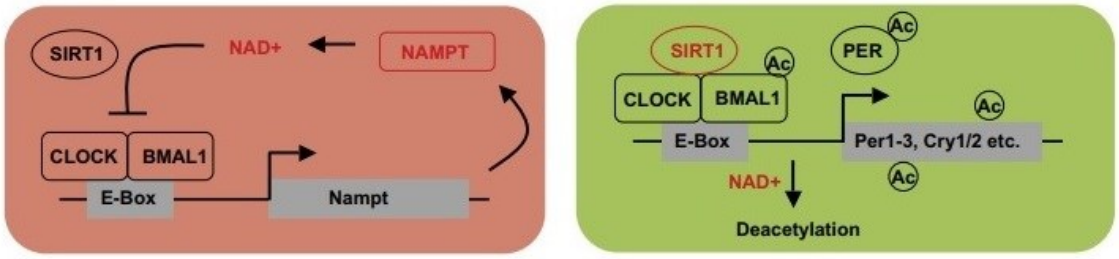

Fig. 5 – An overview of SIRT1 activity in metabolism-sensitive circadian clock regulation (reviewed in Jordan and Lamia, 2013).

Concerning the connection between cellular redox state and circadian regulation, the diagram in Fig. 5 shows that CLOCK:BMAL1 heterodimer binds to the E-box in the promoter of nicotineamid phosphoribosyletransferase gene (*Nampt*), an enzyme controlling the limiting step in the so called NAD^+ salvage pathway (Yang et al., 2007), activating its transcription. NAMPT boosts NAD^+ levels via nicotineamid to nicotinamide mononucleotide (NMN) conversion (Revollo et al., 2007), which is subsequently adenylated and turned into NAD^+ by cellular nicotineamid mononucleotide adenyltransferases (NMNAT). NAD^+ concentration-dependent SIRT1 impairs the E-box binding ability of CLOCK:BMAL1 heterodimers (Nakahata et al., 2009) by blocking CLOCK-mediated acetylation of BMAL1 on lysine 537, completing the transcriptional feedback loop (Hirayama et al., 2007).

The interplay between CLOCK:BMAL1 and SIRT1 is a crucial circadian regulatory element – SIRT1 binds to CLOCK:BMAL1 in a circadian manner and deacetylates BMAL1 (Nakahata et al., 2008). Afterwards, SIRT1 is capable of PER deacetylation, enhancing the rate of its degradation by exposing formerly acetylated lysine residues, which can be subject to consequent ubiqitination, leading up to proteasomal degradation of PER (Asher et al., 2008).

Unlike SIRT1, which has diverse subcellular localization and deacetylation targets, SIRT6, another member of the sirtuin family, is constitutively connected to the chromatin within the nucleus (Mostoslavsky et al., 2006). In the liver, SIRT6 has been found to recruit circadian machinery to the

chromatin and its function is most likely dependent on sensing fluctuations of cellular metabolites such as NAD^+ or fatty acids (Masri et al., 2014).

The cellular redox state has also been proven to regulate the DNA-binding ability of NPAS2:BMAL1 heterodimer (Rutter et al., 2001). NPAS2 (neuronal PAS domain protein 2) is a functional analogue of CLOCK expressed in mammalian prefrontal brain cortex and together with BMAL1 forms a transcriptional activator for *Per* and *Cry* clock genes (Reick et al., 2001).

In addition to the aforementioned enzymes, CLOCK itself has been recognized to possess histone acetyltransferase (HAT) ability, targeting histone H3 at K9/K14 lysines and remodelling the chromatin in such a way that permits transcription (Doi et al., 2006). There are other histone acetyltrasferases operating within the cell – namely CREB-binding protein (CBP) or p300/CBP-associated factor (PCAF) (Curtis et al., 2004) – acting in cooperation with CLOCK. On the other hand, there is a number of histone deacetylases countering their effects, for example PER is capable of SIN3A-HDAC recruitment, *Per1* promoter histone deacetylation and transcription repression (Duong et al., 2011).

2.3 Heme-sensitive REV-ERB proteins and *Bmal1* expression

As stated in chapter 1.2, REV-ERBα is nuclear receptor capable of repressing the expression of *Bmal1* via nuclear repressor coreceptor-histone deacetylase 3 (NCoR-HDAC3) recruitment and constitutes the link between the positive and the negative arm of circadian clock (Preitner et al., 2002). REV-ERBβ is a closely related homologue of REV-ERBα and together these two clock elements coordinate metabolic functions chiefly in the liver (Bugge et al., 2012).

REV-ERBs have been discovered to possess a specific ligand binding domain (LBD), which reversibly binds heme. Through heme REV-ERBs can sense the cellular redox state and also the presence of gases like NO (nitric monooxide) or CO (carbon monooxide), which bind to the LBD and modulate the association of various corepressors with REV-ERBs (Pardee et al., 2009). Considering the fact that heme levels exhibit circadian oscillations (Thöny-Meyer, 1997), REV-ERBs function as physiological sensors of heme concentration with heme being indispensable for their repressor activity (Raghuram et al., 2007). The association between REV-ERBα and NCoR-HDAC3 is directly dependent on heme concentration (heme stabilizes the REV-ERBα corepressor complex) and its experimental depletion led to an apparent increase in *Bmal1* expression (Yin et al., 2007).

2.4 JARID1a, histone deacetylation and demethylation

JARID1a, a histone lysine demethylase containing the JumonjiC (JmjC) and ARID domains, forms a complex with CLOCK:BMAL1, inhibits histone deacetylation caused by histone deacetylase 1 (HDAC1) at *Per* transcription site and significantly enhances the expression of *Per*. *Jarid1a*

knockout reduces the amount of endogenous PER2, shortening the oscillation period (DiTacchio et al., 2011).

Besides its HDAC-inhibitory function, JARID1a also possesses histone demethylase activity, which is common among JumonjiC domain-containing enzymes. This activity is dependent on the presence of two cofactors – α-ketoglutarate and Fe II (Tsukada et al., 2006), which might indicate that JARID1a could be a metabolic state-dependent element connecting the circadian clock with cellular metabolism. However, the capability of related demethylases to influence circadian machinery has been so far discovered only in plants (Lu et al., 2011) and it remains to be examined whether it is actually present in animals as well.

Histone methylation also plays a role in CLOCK:BMAL1-regulated *Per* expression – EZH2 (enhancer of zeste homolog 2) histone methylase forms a complex with CLOCK:BMAL1, catalyses the methylation of lysine 27 on histone 3 at the site of *Per* promoters and subsequently enhances the repressive effect of cryptochromes on clock gene transcription (Etchegaray et al., 2006). Another important enzyme, MLL1 (mixed lineage leukemia 1), which is a histone 3 lysine 4 trimethylase (Hess, 2004), also associates with CLOCK:BMAL1 heterodimer and facilitates its periodic recrutiment to circadian gene promoters (Katada and Sassone-Corsi, 2010).

2.5 Nuclear receptors, nutrition and circadian clock

Nuclear receptors (NRs) are ligand-sensitive proteins acting as transcription factors including classic endocrine receptors binding steroid or thyroid hormones (Evans, 1988) and the so called orphan nuclear receptors with formerly unknown functions. The orphan receptor family includes peroxisome proliferator-activated receptors (PPARs), which have been mentioned in chapter 1.3.3 as an important factor in adipogenesis. PPARα has been first discovered to be a receptor for fatty acids or their metabolic derivatives, including lipids of dietary origins (Issemann and Green, 1990), which also governs general transcriptional response to fasting via hepatic fatty acid oxidation activation (Kersten et al., 1999). PPARγ regulates fatty acid storage in adipose tissue (He et al., 2003). The expression of PPARs exhibits circadian rhythms characteristic for different tissues (Yang et al., 2006). In this sense, PPARs can be viewed as nutrient-sensitive elements constituting yet another link between nutrition, metabolism and circadian clock – the expression of PPARγ, which has been described as a nutrient sensor located in metabolic tissues (Spiegelman, 1998), is fat-intake driven. High fat diet is a potent circadian reprogramming agent and stimulates the expression of PPARγ, which in turn mediates the transcription of several fat-specific genes like phosphoenolpyruvate carboxykinase, a mediator of glycerol synthesis (Vidal-Puig et al., 1996; Tontonoz et al., 1995). A more recent study has revealed a connection between hepatic NRs, including PPARα, and gut microbiome influencing circadian gene expression and overall metabolism in the liver (Montagner et al., 2016).

PGC-1α, a nutrient-responsive transcriptional coregulator of PPARs, also constitutes an integrative element between external cues and metabolism. Its expression oscillates in phase with *PPARα* and other nuclear receptors, and this coordination is crucial for the expression of certain downstream genes (Yang et al., 2006). PGC-1α has been found to interact with ROR orphan nuclear receptors, such as RORα and RORγ, and significantly increase ROR-mediated *Bmal1* transcription, a phenomenom necessary for normal circadian rhythms, as well as *Rev-erb* expression. On the other hand, its activity is regulated by REV-ERBα, which represses the stimulatory effect of PGC-1α on *Bmal1* promoters via corepressor proteins recruitment, forming a negative feedback regulatory loop (Liu et al., 2007).

In addition to the aforementioned NRs, the response of glucocorticoid receptors (GRs) to glucocorticoids can be altered by cryptochromes (CRY1 and CRY2), which interact with GRs and generally repress their functions. On a genetic level, CRY proteins bind to the glucocorticoid responsive element (GRE) in the promoters of specific metabolic genes like the phosphoenolpyruvate carboxykinase gene and repress their transcription (Lamia et al., 2011).

3. Food as a *zeitgeber*

While chapter 1.3 focused on the effects of the circadian clocks on peripheral organs and metabolic cycles taking place therein, the following chapter will describe the impact of external cues like food availability and its composition on the circadian machinery. As stated above, food is a very potent *zeitgeber* capable of uncoupling the expression of circadian genes on the periphery from their expression in the SCN (Damiola, 2000). There are basically two ways for food to influence mammalian circadian clocks – either through food intake timing or via the effect of specific nutrients (summarized in the schematic below – Fig. 6).

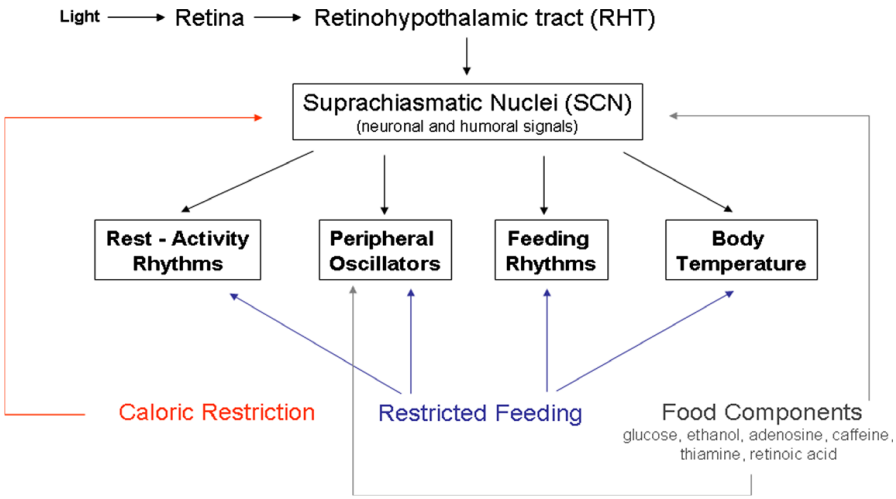

Fig. 6: A diagram elucidating the links between circadian clocks and feeding-related cues (reviewed in Froy, 2007).

3.1 Feeding regimens, diets and their impact on circadian clock

The change in feeding pattern influencing the circadian clock machinery is restricted feeding (RF), which limits the availability of food to a particular time frame without limiting its caloric content (Hall et al., 1953). Mice subjected to RF with food available during the daytime not only adapt their feeding and anticipatory behaviour (increase in locomotor activity prior to the time of feeding) to this limitation (Grasl-Kraupp et al., 1994; Boulamery-Velly et al., 2005), but changes occur at the molecular level as well. RF has been found to advance the phase of liver peripheral clock by 6-12 hours (Hara et al., 2001). RF also disrupts the circadian expression of *Per1* gene in mice with hepatocellular carcinoma, shifting the phase by 3 hours (Davidson et al., 2006), and alters the expression of *Bmal1* and *Rev-erbα* in mice with Glasgow osteosarcoma, countering the disruptive effect of jet lag and even slowing tumor growth (Filipski et al., 2005). On the other hand, RF with food available during the active phase, i.e., during the nighttime in nocturnal animals, normalises clock gene expression, improves the metabolic state and may even prevent the development of metabolic disorders and cancer (Kudo et al., 2004; Chung et al., 2016).

Caloric restriction (CR) procedure decreases the calorie intake by approximately one third of the *ad libitum* (the amount a specimen would eat with free access to food and water) intake (Huseby et al., 1945). CR has been proven to extend the lifespan of test subjects most likely due to increased oxidative damage resistance in brain, heart and skeletal muscles (Sohal and Weindruch, 1996). In addition, contrary to the aforementioned restricted feeding, CR is capable of entraining the clockwork system in the SCN, shifting the phases of *Per1, Per2* and *Cry2* oscillation and altering the expression of these clock genes pursuant to light exposure – CR impairs light-induced transcription of *Per1* and conversely enhances light-induced transcription of *Per2* (Mendoza et al., 2005).

Intermittent fasting (IF) protocol restricts the availability of food to every other day (Anson et al., 2003). The timing of food availability has been found to be the crucial element responsible for the effects of IF on circadian clocks in mammals – daytime IF leads to high nocturnal activity and a severe decline in liver clock genes oscillation, nighttime IF does not (Froy et al., 2009). A recent study shows that IF disrupts the expression of *Clock* and through *Clock*-facilitated human gluccocorticoid receptor acetylation can lead to abnormal diurnal cortisol fluctuations, hypercortisolism and even metabolic syndrome (Ajabnoor et al., 2017).

A general high-fat diet administered to mice severely attenuated *Clock* oscillation in fat tissue, lowered the amplitude of *Bmal1* expression in fat and liver tissue and also altered the expression pattern of nuclear receptors such as RORs and PPARs (Kohsaka et al., 2007) – this phenomenon was more closely described in chapter 2.5. Ketogenic diet, which is high in fatty acids and low in carbohydates and proteins, resembles the conditions of caloric restriction and it is used as a mean to combat obesity or type 2 diabetes (Astrup et al., 2004). The diet has been discovered to abnormally enhance circadian expression of PAI-1 (plasminogen activator inhibitor 1) which may increase hypofibrinolytic risk and be detrimental to cardiovascular health (Oishi et al., 2009). High fat diet also shifts the recruitment of CLOCK and BMAL1 to chromatin at target promoters, causing, among other things, the impairment of NAD^+ levels cycling through lowered NAMPT (nicotineamid phosphoribosyletransferase) expression (Eckel-Mahan et al., 2013).

3.2 The effects of specific food components on circadian clock

Apart from the influence of the general metabolic state of the cell on circadian machinery, which was the focus of chapter 2, the particular food components, or nutrients, may entrain the circadian clock as well.

3.2.1 Glucose

According to experiments using streptozotocin-induced diabetic rats, high glycemia leads to a phase shift in the expression of clock genes in the peripheral oscillator of the heart (Young et al., 2002). Glucose has also been discovered as the triggering agent of *Per1* and *Per2* mRNA levels down-regulation in rat fibroblasts; two transcription regulators, TIEG1 (TGFbeta inducible early gene-1) and

VDUP1 (vitamin D3 upregulated protein 1), have been identified as glucose-responsive factors responsible for circadian resetting – TIEG1 is capable of *Bmal1* and *Per1* transcription repression and VDUP1 shuts off the activity of CLOCK:BMAL1 heterodimer, subsequently reducing the expression of *Per* genes (Hirota et al., 2002). Glucose-solution administration to Wistar rats also managed to phase shift the expression of *Per2* gene in the SCN (Iwanaga et al., 2005).

3.2.2 Amino acids and protein

In regard to the impact of amino acids on the circadian clock, a recent study revealed the effect of L-ornithine dietary intake on peripheral circadian machinery – it advanced the phase of *Per2* expression by approximately 2 hours in mice, albeit indirectly via insuline secretion stimulation (application of L-ornithine on embryonic fibroblasts directly did not induce such a shift) (Fukuda et al., 2016). There have also been studies on whether calculated intake of tryptophan, a precursor of serotonin and melatonin, could counter age-related circadian clock deterioration with the conclusion that it actually may improve sleep quality in older animals; however, this research has been carried out on ring doves, therefore the effect of tryptophan on mammalian circadian clock remains untested (Garau et al., 2006). Besides that, a recent analysis examined the effect of general protein-restricted maternal diet on male mice offspring and discovered that it caused anxiety-related shifts in behaviour and disrupted sleep patterns, but did not prove that such diet would impair circadian rhythms in adult animals (Crossland et al., 2017).

3.2.3 Fatty acids

Concerning the effect of fatty acid (FA) intake on circadian rhythms, a differential impact of saturated FAs and polyunsaturated FAs on the expression of *Bmal1* in a murine hypothalamic cell line has been discovered. Palmitate (a very common unsaturated FA) intake leads to an increase in *Bmal1* transcription, whereas consequent docosahexaenoic acid (DHA, an omega-3 polyunsaturated FA) intake dampens the disruptive effect of palmitate on circadian clock (Greco et al., 2014). In addition to that, fish oil high in both DHA and EPA (eicosapentaenoic acid) content strengthens the circadian phase shift in the liver induced by restricted feeding and stimulates *Per2* gene expression (Furutani et al., 2015).

3.2.4 Other dietary elements

There is also a number of non-essential dietary elements with the capacity to impact circadian clock synchronization in mammals, for example caffeine, alcohol, polyamines and polyphenols. Caffeine-infused food provided to mice *ad libitum* advances the phase of liver clock genes oscillation and decreases the oscillation amplitude of clock genes in the jejunum; aside from that, the same experiments on HEK-293 cell culture proved that caffeine generally increases the expression of *Clock* and *Bmal1* genes (Shearman et al., 1997). Furthermore, chronic alcohol consumption has been found to significantly reduce the expression of clock genes and severely disrupt the parameters of circadian

rhythms (Huang et al., 2010). Polyamines like spermidine or putrescine, which take part in transcriptional, translational and cell growth processes, possess the ability to control circadian rhythms through PER2:CRY1 interaction enhancement. Their increased dietary intake can also counter the circadian period lenghtening caused by natural decline in polyamine levels occuring in high age (Zwighaft et al., 2015). Resveratrol (3,5,4′-trihydroxystilbene), which is a natural polyphenol found in various plants, lengthens the lifespan and generally improves health and survival of mice via *Bmal1* and *Per* expression regulation and SIRT1/PGC-1α activation (Baur et al., 2006; Oike and Kobori, 2008).

4. The relationship between metabolic disorders and circadian clock

The last chapter of the thesis will associate the aforementioned mechanisms of food-driven circadian clock entrainment with metabolic health and describe the implications of circadian disruption for the two most common metabolic disorders – obesity and diabetes. Generally speaking, all the peripheral clocks of mammalian circadian system have to be synchronized with the SCN and coherent in phase, otherwise any disruption in sleep/wake behaviour, feeding patterns or metabolic cycles can constitute basis for a metabolic disease. For example, sleep deficiency and concurring sleep-disordered breathing has been directly linked to glucose metabolism impairment, insulin resistance and therefore higher risk of obesity and diabetes (Punjabi et al., 2004). The same can be said for shift work, social jet-lag, stress, overconsumption of food or improper food intake timing – all symptoms of a modern lifestyle (Barbadoro et al., 2013; Blasiak et al., 2017; Espitia-Bautista et al., 2017).

One of the first studies on the relation between circadian clock and metabolic diseases found out that *Clock* mutant mice exhibit severely altered food intake patterns, lowered overall energy expenditure and particularly increased body weight due to a higher percentage of visceral fat in comparison with wild type specimens. The mutant animals were also hypercholesterolemic, hypertriglycerdemic, hyperglycemic and hypoinsulemic (Turek et al., 2005). On the other hand, according to a later research, $Clock^{\Delta 19}$ mutation lowered the concentration of fatty acids in blood, increased insuline sensitivity and did not cause obesity (Kennaway et al., 2007). Furthermore, several experiments proved a significant correlation between various single nucleotide polymorphisms (SNPs) in the *Clock* gene and proneness to obesity and metabolic syndrome (Sookoian et al., 2008; Garaulet et al., 2009). Other clock gene mutations can be causes of obesitogenic behaviour as well – specific polymorphisms in the *Per2* gene have been linked with needless snacking, eating out of boredom and skipping breakfast – all possible roots of concurring abdominal obesity (Garaulet et al., 2010).

Obesity is a major risk factor in the development of type 2 diabetes, which can be also caused by pancreatic circadian machinery disruption (Gale et al., 2011). As stated in chapter 1.3.2 dealing with pancreatic circadian clock, global *Clock* and *Bmal1* mutations have universally suppresive impact on gluconeogenesis and adipogenesis (Rudic et al., 2004; Shimba et al., 2005), whereas liver-specific *Bmal1* deletion leads to fasting hypoglycemia, excessive glucose clearance and disrupts the oscillation of hepatic regulatory genes (Lamia et al., 2008). Various mutations of other clock genes such as *Cry, Per*, and *Rev-erbα* have also been found to disruptively influence carbohydrate and lipid metabolisms and possibly contribute to diabetes (Barclay et al., 2013; Grimaldi et al., 2010; Lau et al., 2008). *Clock* and *Bmal1* mutations in pancreatic islet impairs their growth, insulin secretion and lowers the expression of genes involved in glucose metabolism (Marcheva et al., 2010). *Rev-erbα* mutation in

pancreatic islets disrupts glucose-driven insulin release and blocks cell growth as well (Vieira et al., 2012).

Food intake timing can be both detrimental and beneficial for general metabolic health – restricting food availability only to the resting phase disrupts the synchronization between the master clock in the SCN and peripheral clocks and leads to overall weight gain (Arble et al., 2009). The molecular mechanism of this phenomenon includes many of the previously mentioned clock-controlled elements such as PPARα, CREB and REV-ERBα and ultimately leads to a 12 hour peripheral clock phase shift (Mukherji et al., 2015). On the other hand, limiting the food availability to the active phase can counter the negative effects of this misalingnment, preventing weight gain and even obesity in the long run (Salgado-Delgado et al., 2010). Specific diets are also capable of chronodisruption – a generally high-fat diet is dangerous not only because of its large caloric content, but has been proven to alter the circadian expression of several pancreatic clock genes, change the oscillations of insulin secretion and potentially increase the risk of type 2 diabetes development as well (Vieira et al., 2012).

In order to maintain healthy weight and prevent metabolic disease it is crucial to avoid circadian misalignment caused by desynchronization between feeding/fasting and light/dark cycles (Scheer et al., 2009). Research on the impact of food intake timing on weight loss proved that late lunch eaters were much more frequent carriers of aforementioned *Clock* SNPs associated with obesity, displayed a generally lower rate of weight loss, whereas there were no significant disparities in overall energy intake and expenditure between these late eaters and early eaters (Garaulet et al., 2013). A feeding pattern with a breakfast rich in calories and a modest dinner is greatly beneficial for glucose, insulin and triglyceride levels and eventual weight loss in comparison with a diet where there is only a small breakfast and most of the daily caloric intake is consumed in the evening (Jakubowicz et al., 2013). Restricting the daily food intake only to a time frame of 10 to 11 hours leads to significant weight loss as well as an improvement in sleep quality (Gill and Panda, 2015).

Conclusion

The aim of this thesis was to summarize existing knowledge and research in the field of molecular chronobiology and chrononutrition, which remains a very relevant scientific topic due to its implications for human health. Food has a well documented impact on mammalian circadian clock, being a very influential *zeitgeber* capable of disconnecting the oscillation of clock genes on the periphery from their counterparts in the SCN. Because clock genes often function as expression regulators for various important genes involved in metabolic pathways, such circadian desynchronization can have severe effects on universal energy homeostasis and metabolic health of the organism. There are many dietary regimes and feeding patterns to which people adhere either out of necessity, habit or as a medical precaution. These often involve variations in temporal availability of food, overall caloric content or nutrient composition. Research managed to prove that such alterations in food intake can influence the expression of clock genes in both disruptive and restorative manner, with certain nutrients capable of countering the adverse impact of other food components or unsuitable feeding regimes on the circadian system. This is the direction in which chronobiology should in my opinion continue its scientific effort in order to expand the knowledge of the beneficial effects of nutrients on human circadian clock.

Since there is a direct link between circadian clock and metabolism, even small disruptions in the molecular clockwork possess the potential to negatively influence metabolic health and ultimately cause a metabolic disease such as obesity and possibly concurring type 2 diabetes. Recent studies indicate that modern lifestyle, rich in sleep deficiency, inappropriate food timing and unhealthy diets, might be among chief causes of various aspects of metabolic syndrome. On the other hand, the elimination of risky behaviour and focus on proper feeding in accordance with wake and sleep cycles may present a potential remedy to at least some cases of metabolic disorders, which is why research in the field of nutrition-related chronobiology is crucial in the attempt to maintain the metabolic health of both the population and individuals.

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