Circadian Influences on the Auditory System

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4.1 Introduction

In this chapter, we will deal with circadian rhythms and their influence on hearing and tinnitus. Circadian rhythms control bodily functions such as sleep, inflammation, metabolism, renal function, hormone secretion, as well as auditory functions. Animal studies have revealed that the auditory system has an inbuilt clock machinery that regulates sensitivity to noise throughout the day. Due to the detrimental consequences of disrupted circadian rhythms on human health (e.g., jet lag, shift workers), it is important to understand how the clock system regulates auditory function with the aim of providing new avenues for the development of targeted therapies.

4.2 Circadian Rhythms

4.2.1 What Are They

Circadian rhythms ("circa *diem*" meaning "approximately a day") are among the most conserved systems of biological function, already emerging in light-sensitive bacteria and evolving into complex internal timing systems in mammals. Sensing periodic changes has allowed almost all organisms (from cyanobacterias, fungi, green plants, metazoans, to mammals) to adapt their behavior and optimize their physiological functions to changes in the external environment (Paranjpe and Sharma 2005). The synchronization of the rhythmic entrainment by regular daily events, such as light/dark cycles, temperature, or humidity variations, facilitates the

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anticipation of these predictable changes, maximizing ecological fitness—meaning the ability to adapt to a given environment.

Circadian rhythms enable synchronization of the rhythmic entrainment by regular daily events, such as light/dark cycles, temperature, or humidity variations.

These external and rhythmic environmental cues (inputs) are called *zeitgebers* (German for "time-giver"). In the same way that metronomes help musicians internalizing the sense of tempo, these *zeitgebers* influence biological clocks to facilitate the internal representation of time and anticipate predictable consequences of rhythmic events. The most important *zeitgebers*, in addition to the light-dark cycle and temperature mentioned above, are also found food consumption and social interactions (Davidson and Menaker 2003; Lowrey and Takahashi 2004).

In mammals, most physiological processes are subjected to temporal regulations (Dibner et al. 2010). These include cerebral activity (sleep and wake cycles), feeding behavior, metabolism and energy homeostasis, immune responses, heart rate, blood pressure, renal activity, hormonal and cytokine secretion, detoxification, and, recently, auditory functions (Meltser et al. 2014). In anticipation of a resting period, the temperature of the body falls, glucocorticoids decrease, anabolism increases, and melatonin is secreted. Reversely, in preparation of the high demands of daily activities, the opposite phenomenon occurs. In modern societies, disruptions of the alignment of body functions with the environmental cycle are seen in shift and night works, reductions in sleep time and sleep deprivation, travel, and jet lags. The understanding of the consequences of circadian arrhythmia and their mechanisms has emerged from studies of mutant animal models with altered rhythms.

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4.2.2 Organization of the Circadian System

Three levels of organization characterize the circadian system (Fig. 4.1): (1) inputs by which the environment communicates information to the internal master clock located in the brain, namely, the suprachiasmatic nucleus (SCN); (2) factors that contribute to brain-dependent outputs such as sleep onset, sleep-wake cycles, and other CNS-dependent behavioral changes; and (3) peripheral outputs that are the physiological consequences of the coordinated hormonal, metabolic, immune, thermoregulatory, and autonomic nervous functions. Most organs and, hence, most cells, have their own biological clocks. These cellular and organ clocks have their

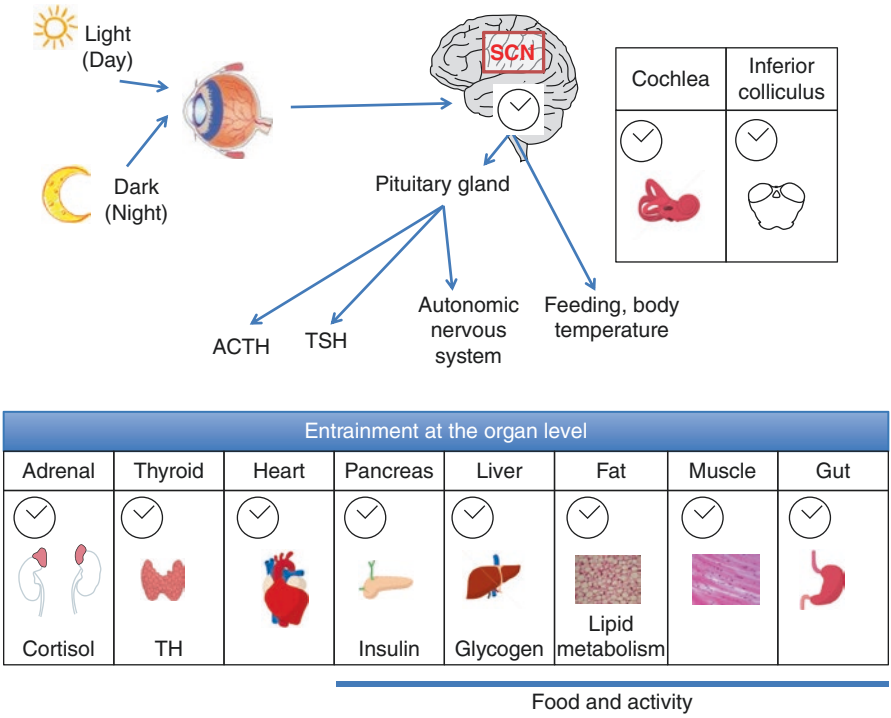

Fig. 4.1 Peripheral clocks and regulation of circadian physiology. The suprachiasmatic nucleus (SCN) is the major pacemaker of the circadian system that receives photic information directly from the retina and synchronizes peripheral oscillators found in other brain areas and peripheral tissues (entrainment). This is mediated by autonomic innervation, humoral signals, hormones, and the regulation of body temperature and feeding. Modified from Hickie et al., BMC Medicine, 2013, 11:79 with permission from BMC journals

own phase with respect to their own physiological duties. This is where the master clock aligns cellular and organ clocks to the external 24 h light-dark cycle in order to form a coherent pattern of behavioral and physiological rhythms.

Prior to describing the recent identification of clock systems in the auditory pathway, we will review general aspects of the structure and function of the mammalian circadian system.

4.3 Molecular Biology of Circadian Rhythms

4.3.1 Core Clock Genes

As evolution has progressed into more and more complex organisms, the biological clocks have incorporated more subtle mechanisms of regulation to incorporate the timing cues of a variety of *zeitgebers* and produce a variety of biological functions.

A major advance in the circadian field was the concept that biological rhythms are generated at the level of molecules that constitute autoregulatory feedback loops that self-regulate their transcription within a 24 h period. This process, which ballpark is conserved across various phylae, involves a series of activators that promote the transcription of repressors, which protein products translocate back in the nucleus to inhibit the transcription of the initial activators. The subsequent decrease of activator mRNA transcription reduces the level of inhibitory protein production, releasing the transcriptional machinery from its molecular breaks, thereby reinitiating the cycle.

In mammals, the circadian machinery has evolved into a complex cellular process to incorporate a large number of cues. The molecular clock can be paralleled to the machinery of normal clocks, with core large clocks regulating the rhythms of the smaller clocks. The molecular clock machinery is based on two interlocked autoregulatory transcriptional/translational feedback loops (TTFL) (Albrecht 2002; Kondratov et al. 2007; Lowrey and Takahashi 2004). In the center of the feedback loops, two basic helix-loop-helix (bHLH) transcription factors, CLOCK and BMAL1, dimerize and bind to E-box elements at the promoter regions of negative-feedback genes called *Period* (*mPer1* and *mPer2* in the mouse) and *Cryptochrome* (*mCry1* and *mCry2*) to trigger their transcription. The CRY and PER protein products dimerize and form large corepressor complexes. As their concentration increases, they bind to CLOCK/BMAL1 complexes thereby interfering with its transcriptional regulation. The attenuation of their own transcription leads to a decrease in CRY and PER proteins. With a short life cycle, the decrease in PER-CRY complexes no longer interferes with CLOCK-BMAL1 heterodimers, and a new cycle of PER and CRY generation can follow (Fig. 4.2a).

An additional "interlocking" loop consists of ROR (RORα, RORβ, and RORγ) and REV-ERβ (REV-ERβα and REV-ERβ) proteins that are activated by the CLOCK/BMAL1 dimers. The resulting activated proteins recognize RORE response elements (RREs) within the promoter region of *Bmal1* and *Clock* genes to regulate their transcription. RORs activate *Bmal* and *Clock* transcription, whereas REV-ERβs recruit the corepressor NCoR1 to inhibit gene transcription (Fig. 4.2b). Overall, the rhythmic regulation of *Bmal1* transcription is thus typically in anti-phase with that of *mPer*, *mCry*, and *mREV-ERβ* mRNAs.

Disruption of both *mPer* genes, or both *mCry* genes, causes immediate behavioral arrhythmicity when the double knockout animals are placed in constant darkness (meaning in the absence of light entrainment), showing the essential role of PER and CRY in the maintenance of a functional clock (van der Horst et al. 1999; Zheng et al. 2001). Single mutants show continued clock oscillations indicating that there is partial compensation among family members.

Outside the core clock elements are found the clock-controlled genes, which output function is to control diverse physiological functions (Fig. 4.2c). The mechanism of regulation of clock-controlled genes resembles a lot to that of the core clock as suggested by the identification of main regulatory motifs of rhythmically expressed clock-controlled genes: E-boxes, D-boxes, and cAMP-responsive

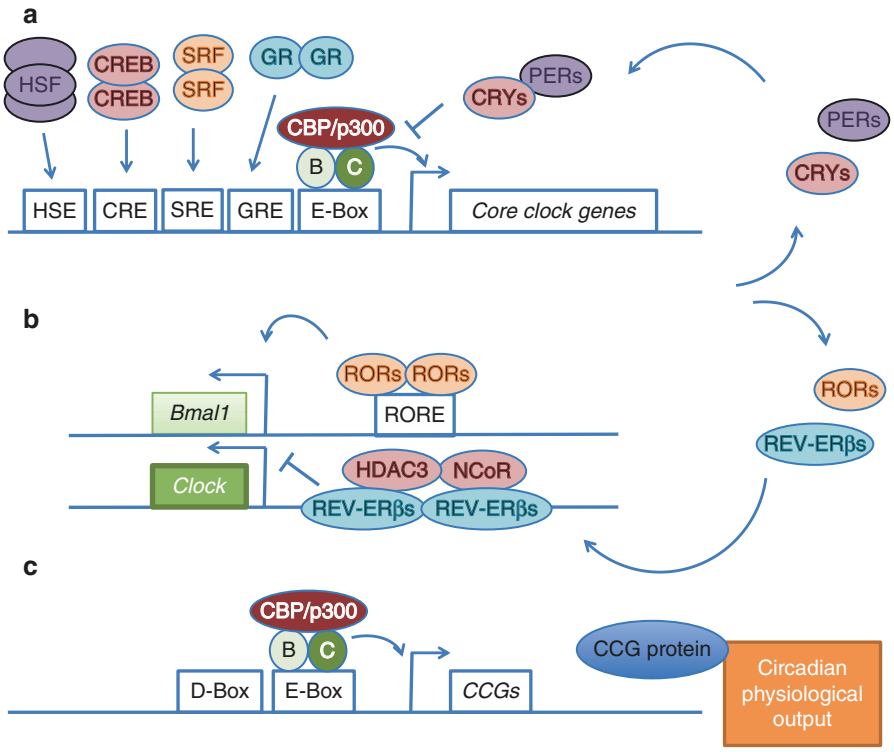

Fig. 4.2 The molecular clock machinery. (**a**) *Core loop*: a complex of CBP/p300, CLOCK (C), and BMAL1 (B) binds to E-box on the promoter of *Per* and *Cry* genes (*Per1*, *Per2*, *Cry1*, and *Cry2*) to induce their transcription. Accumulation of PER/CRY complexes inhibit CLOCK and BMAL1 complexes, thereby repressing their own transcription. The progressive decline of PER and CRY proteins allows CLOCK and BMAL1 to initiate a new cycle of gene expression. *Per1* and *Per2* transcription can be additionally modulated by additional tran: heat shock factor (HSF) binding to heat shock elements (HSEs), cAMP-responsive element (CRE)-binding protein (CREB), and glucocorticoid receptor (GR) binding to glucocorticoid-responsive elements (GRE). (**b**) *Interlocking loop*: CLOCK and BMAL1 also trigger the expression of the orphan nuclear receptor genes *Ror* (*Rorα*, *Rorβ*, and *Rorγ*) and *Rev-Erβ* (*Rev-Erβα* and *Rev-Erβ*). The transcription of *Bmal1* and *Clock* is regulated through competition between REV-ERβ repressors and ROR activators, acting on retinoid-related orphan receptor response elements (RORE). (**c**) *Regulation of clock-controlled genes (CCGs):* CLOCK and BMAL1 can regulate the transcription of CCGs by binding to E-box elements on their promoter area. These genes then are translated into CCG protein products and regulate physiological processes in a temporal way. Modified from Basinou et al., Hearing Research, 2016, in press with permission from Elsevier

element (CREs) (Bozek et al. 2009, 2010; Korencic et al. 2014). For example in the liver, transcription factors of the bZIP family (DPB, TEF, and HLF) bind to D-boxes in the promoter area of the aldosterone receptor (*CAR*) gene, which in turn regulates the rhythms of detoxification via ALAS1 and cytochrome P450 expression (Gachon et al. 2006).

The accurate coordination of these transcriptional/translational feedback loops requires the tight control of posttranscriptional and posttranslational loops to generate a 24 h periodicity. Accumulating evidence shows that the activation and the stability of the core clock proteins is regulated by phosphorylation/dephosphorylation, SUMOylation, ubiquitination, acetylation/deacetylation, and polyADP-ribosylation (Dibner et al. 2010; Mehra et al. 2009). Even, it has been found that circadian rhythms of some specific metabolic functions such as peroxiredoxins in the absence of transcription (Edgar et al. 2012; O'Neill et al. 2011). At a broader scale, hormones, temperature, neurotransmitters, and second messengers (Dibner and Schibler 2015) also interfere with the expression of core clock genes such as *Period*, which allows resetting the phase of the core clock rhythms according to systemic cues.

At a broader scale, hormones, temperature, neurotransmitters, and second messengers also interfere with the expression of core clock genes.

It is interesting to note that near 10–20% of mRNA transcripts display circadian patterns of expression depending on the organ (Akhtar et al. 2002; Hughes et al. 2009; Panda et al. 2002; Storch et al. 2002; Ueda et al. 2002) but that 50% of rhythmic liver proteins are encoded by nonrhythmic mRNA transcripts (Mauvoisin et al. 2015), emphasizing the importance of translational and posttranslational modifications for the control of clock output pathways.

4.3.2 From Molecules to Physiology

A number of signals regulate the core clock and interfere with the rhythms of clock-controlled genes. This allows the cellular systems to respond in a timely manner to environmental changes with specific physiological outputs. As a consequence, cellular clocks appear ubiquitously present throughout the mammalian body (Yoo et al. 2004). Within a tissue, an ensemble of cellular clocks—although not all in synchrony—generate a coherent rhythmic physiological function. For all tissues to perform their functions on time, a master clock is needed to harmonize body rhythms. Located in the hypothalamus around the third ventricle, near 2000 neurons in rodents form the suprachiasmatic nucleus (SCN) that orchestrate the circadian system. The SCN was named the master clock after lesion and grafting studies demonstrated it is necessary and sufficient for the generation of body rhythms (Moore and Eichler 1972; Ralph et al. 1990; Stephan and Zucker 1972).

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Interactions between these neurons through chemical coupling and gap junctions facilitate their synchronization (Davidson and Menaker 2003), making the rhythms of the SCN robust enough to act as a pacemaker of all body rhythms. The SCN is entrained by light captured by the retina (Fig. 4.1), where intrinsically photoreceptive retinal ganglion cells (ipRGCs), which express melanopsin, project photic signals to the SCN via retinohypothalamic fibers (Hannibal and Fahrenkrug 2002; Hattar et al. 2002). This was evidenced in elegant genetic studies in mice, whereby the loss of these few hundred cells still allowed normal vision but not the synchronization of body rhythms to light input (Guler et al. 2008). Specific neurons (VIP) from the SCN transpose the electric signals to the cellular clock, through the activation of Ca^{2+}-dependent kinase/CREB signaling cascades that initiate the cycles of molecular rhythms by triggering *Per* gene expression (Dibner et al. 2010). Neuronal interactions spread the rhythmic information across the SCN, which robust and synchronized output signals orchestrate central (e.g., olfactory bulbs and hippocampus) and peripheral tissues (e.g., liver, muscle, and adrenal glands) (Guilding and Piggins 2007; Richards and Gumz 2012).

The communication between the SCN and the other clocks occurs through autonomic innervation and to a second degree through the regulation of systemic cues such as body temperature, hormonal signaling, and feeding (Mohawk et al. 2012) (Fig. 4.1). In return, peripheral clocks provide feedback to the SCN regarding the internal status of the body by means of hormones and metabolites. A continuous and effective communication between external and internal signals allows to produce a coherent rhythmic physiological output.

Whereas the SCN is mainly entrained by light, peripheral clocks are regulated by signals either directly or indirectly controlled by the SCN. The SCN can directly influence peripheral rhythms thanks to the secretion of key factors such as prokineticin 2 (PK2) that can directly regulate locomotor activity rhythms (Cheng et al. 2002) and VIP that regulates core clock gene expression down to the liver and adrenal glands (Loh et al. 2011). Autonomic innervation plays an important role in the indirect communication between the SCN and peripheral clocks. For instance, the SCN projects efferent toward the paraventricular nucleus to control glucose homeostasis in the liver or glucocorticoid secretion by the adrenal glands (Ishida et al. 2005; Kalsbeek et al. 2004). Glucocorticoids (GCs) are of particular interest since they are powerful synchronizers of circadian rhythms. Glucocorticoid receptors are ubiquitously expressed nuclear receptors that recognize glucocorticoid response elements (GRE) present in the promoter and enhancer regions of core clock genes and clock-controlled genes. The glucocorticoid synthetic agent dexamethasone (DEX) is a well-known drug to synchronize circadian rhythms in culture.

Clocks from the heart, kidney, pancreas, lung, and thyroid glands are also controlled by autonomic nervous connections.

Rest and activity cycles drive feeding and body temperature rhythms that are additional zeitgebers. For instance, feeding cycles are important zeitgebers in the liver, the pancreas, the heart, and the kidneys (Dibner et al. 2010), possibly through glucose-sensing pathways and sirtuin signaling (Gachon et al. 2004a). Changes in

body temperature (1–4 °C) can reset peripheral clocks via heat shock factor 1 (HSF1), which also regulates core clock gene expression through the binding to heat shock response elements (Reinke et al. 2008). However, it is thought that the robust rhythms from the SCN make it resistant to feeding and temperature changes (Abraham et al. 2010). Imposed feeding schedules in mice during resting phase can completely invert the circadian rhythms of peripheral tissues, while the SCN remains unaffected. These experiments also show that feeding cues can dominate hormonal signals (Abraham et al. 2010). Once normal feeding schemes are provided, the phase of the tissues resets in 2–3 days showing that the SCN can rapidly take over its role as a master clock. The importance of the SCN in synchronizing peripheral rhythms has been evidenced in lesion experiments where, in absence of the SCN, peripheral tissues became desynchronized with time (Yoo et al. 2004). It is now very well established that the SCN acts as a conductor of an orchestra, whereby peripheral tissues respond to the director's instructions to provide a consistent physiological response.

4.3.2.1 The SCN and the Adrenal Glands: Teamwork for Body Synchrony?

If it can be concluded that almost any tissue harbors a circadian machinery, it remains that each organ harbors its own set of molecular elements to coordinate its physiological functions. In a study of Panda and others, the overlap between circadian transcripts in the SCN and the liver (among 650 oscillating transcripts) was compared, and only 28 transcripts were found common to the two tissues (Panda et al. 2002). Few of these 28 genes were core clock genes showing that the control of most circadian genes is highly tissue-specific, each peripheral clock being responsible for a specific output program dependent on the physiological functions.

The control of most circadian genes is highly tissue-specific. Each organ needs to tightly coordinate different functions at different times.

Each organ also needs to tightly coordinate different functions at different times. For instance, the liver is capable of regulating at appropriate times of the day gluconeogenesis and glycolysis, two chemically antagonistic processes. The temporal control of tissue- and time-specific physiological functions is done through the expression of clock-controlled genes that harbor various *cis*-regulatory elements to allow their on or off transcriptional states thereby generating a broad range of time-regulated cyclic activity within the same tissue.

An illustration of how clock-controlled genes are regulated by different *zeitgebers* has been shown in adrenalectomized mice, deprived of circulating glucocorticoids. Near 2/3 of rhythmic liver transcripts lost their rhythmicity in absence of adrenal glands, none of which were core clock genes (Oishi et al. 2005). These glucocorticoid-controlled genes were in a large part encoding liver enzymes (such as glucokinase, HMG-CoA reductase, and glucose-6-phosphatase). This proportion

was replicated in a pharmacological study, in which DEX resynchronized 57% of liver genes from SCN-lesioned animals (Reddy et al. 2007) likely through a mechanism involving GR and CRY interactions (Lamia et al. 2011). Possibly, the SCN controls core clock rhythms, and secondary entrainment cures such as GCs orchestrate the rhythmicity of genes that regulate physiological functions in a given organ.

As such, the adrenal gland emerges as an important relay station downstream of the SCN to synchronize peripheral clock rhythms. Its endocrine functions are regulated in a circadian fashion (e.g., GCs show a rhythmic secretion pattern). The control of GC circadian secretion by the SCN is known from a long time and evidenced by SCN ablations (Moore and Eichler 1972; Stephan and Zucker 1972). In contrast, the pulsatile (or ultradian—see Chap. 2) pattern of GC secretion is independent of the SCN (Waite et al. 2012). The broad range of actions of GCs, from the regulation of stress or immune responses, as well as cognitive functions, suggests that the circadian actions of GCs might serve as key influencers of physiological rhythms. GCs exert their action via the glucocorticoid receptor (GR), expressed throughout the body including the cochlea (Meltser et al. 2014) and the brain—with the exception of the SCN (Balsalobre et al. 2000). GCs also activate the mineralocorticoid receptor (MR). The circadian secretion of GCs is a complex involvement of autonomic innervation controlled by the SCN, the hypothalamic-pituitary-adrenal (HPA) axis, and local adrenocortical clocks.

4.3.2.2 Physiological Functions Controlled by Circadian Rhythms and Their Dysregulation

Transcript analyses using qRT-PCR showed the circadian expression of core clock genes in the heart, lung, liver, stomach, spleen, and kidney (Yamamoto et al. 2004). Using transgenic rats driving luciferase expression under the control of Per1 promoter (*Per1-luc*), tissue explant cultures showed oscillations in the SCN, skeletal muscle, liver, lung, pineal, adrenal, and thyroid glands (Yamazaki et al. 2000, 2009). Another rodent model in which the luciferase-coding sequence was knocked-in the Per2 mouse locus (PER2::LUC) allowed to identify rhythmic oscillations in additional organs such as the cornea, the pituitary, and the retrochiasmatic area (RCA) (Yoo et al. 2004). How circadian cycles of luciferase expression are captured is illustrated in Fig. 4.3. As a consequence, numerous physiological functions manifest daily oscillations including detoxification processes by the liver, the kidney, and the small intestine (Gachon et al. 2006); carbohydrate and lipid metabolism by the liver, muscle, and adipose tissue (Lamia et al. 2008; Le Martelot et al. 2009); renal flow and urine production, blood pressure; and the rate of heart beats (Gachon et al. 2004a). Understanding of the physiological outputs from molecular clocks in each organ derives mainly from functional studies using mice lacking *Bmal1*, either systemically or in a tissue-specific manner, or mice lacking *Per1* and/or *Per2*. For instance, mice lacking *Bmal1* display a complete loss of circadian behavior, metabolic abnormalities, and subsequent reduced life span (Kondratov et al. 2006). *Bmal1* or *Clock* mutants develop diabetes due to reduced insulin secretion by the pancreatic islets (Marcheva et al. 2010), a process specific to β-cells that regulates insulin secretion in a circadian manner (Perelis et al. 2015).

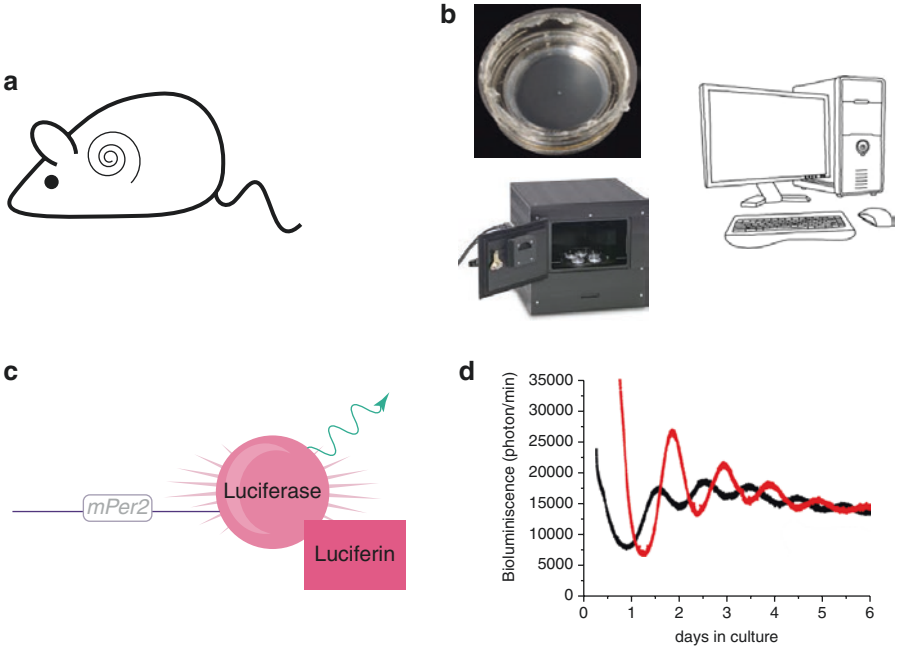

Fig. 4.3 Measures of circadian PER2::LUC oscillations in explant cultures. (**a**) The experimental system to analyze circadian gene expression in explants consists of isolating organs from mice expressing a luciferase fused to Period 2. (**b**) Organ explants are placed on membranes, and real-time bioluminescent imaging of PER2::LUC organs is collected using photomultiplier tubes which is highly sensitive and has low noise. Representative bioluminescence record of circadian PER2::LUC expression in cultured organs is then collected (**c**) and analyzed (**d**) for amplitude, period, and phase

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Altered eating regimes, sleep and wake cycles, as well as medications can potentially alter the synchronicity of different organs and their harmonization at the body level leading to abnormal physiological functions. Shift workers suffer from the chronic desynchronization of their body with the regular environmental cues and of the SCN and peripheral clocks leading to increased prevalence of symptoms of the metabolic syndrome (Evans and Davidson 2013). Despite the fact that the SCN rapidly synchronizes its rhythms to light cues (e.g., in long-distance travelers changing time zones), their organs require more time to readjust their rhythms (jet lag). Underlying the human relevance, polymorphisms in *hPER2 and hCRY2* associate with blood glucose levels. Those in *hCLOCK* are linked with obesity and *hBMAL1* with hypertension and type 2 diabetes (Dibner and Schibler 2015).

4.3.3 Auditory System and Circadian Rhythms

Whether the auditory system harbors a molecular clock was unknown until recently. Several evidences pointed toward such circadian regulation. Firstly, noise can act as a *zeitgeber* to regulate body rhythms (Menaker and Eskin 1966; Reebs 1989). Secondly, outer hair cell function—measured by means of distortion products of otoacoustic emissions—appears to fluctuate throughout the day (Cacace et al. 1996; Haggerty et al. 1993). Thirdly, aminoglycoside-mediated ototoxicity is more damaging at night than during the day (Yonovitz and Fisch 1991). The later could however involve several mechanisms: different rates of liver detoxification around the clock could alter systemic bioavailability; the function of the cochlear blood barrier could fluctuate throughout the day making it more permeable to ototoxic drugs in the night than in the day; finally, the cochlear response to ototoxic insults could be weaker during the night due to varying metabolic rates throughout the day. Our laboratory revealed in an initial study that the cochlea possesses a robust molecular clock that responds differentially to day or night noise stimulation (Meltser et al. 2014). In a second work, we provided evidence that the inferior colliculus (IC), a midbrain relay of the auditory pathway, also has a molecular clock (Park et al. 2016). Here, we describe the findings of these two studies.

4.3.3.1 The Day-Night Susceptibility to Auditory Trauma

The fact that sensitivity to noise also varies at different times of the day was unknown until recently. Awake mice (non-anesthetized) exposed to a noise trauma (6–12 kHz, 1 h, 100 dB SPL) during the night (9 PM) displayed permanent shifts in hearing thresholds measured by auditory brainstem responses (ABRs) 2 weeks after noise trauma, whereas those exposed during daytime (9 AM) recovered to normal hearing thresholds (Meltser et al. 2014). Interestingly, ABRs measured 24 h post-trauma revealed equivalent shifts in hearing thresholds (15–30 dB, from 8 to 24 kHz) in day or night exposed animals. Although distortion products of otoacoustic emissions (DPOAEs) were not performed in this study, cochleograms revealed that no hair cell loss had occurred in both day and night noise groups. These findings suggest that immediate synaptic uncoupling, mainly caused by glutamate excitotoxicity after noise exposure, is similar during the day or during the night. Although levels of glutamate in the cochlea were not measured after day or night noise exposure, no differences were found in the wave I amplitude of the ABR 24 h post-trauma suggesting that animals were exposed to similar levels of sound in this paradigm (unpublished observations). This notion is important since nocturnal animals are more active during the night, whereas they are sleepy during daytime, and the resulting differences in hearing thresholds after day or night noise exposure could be due to varying levels of sound reaching the ear simply because of different behavioral patterns. This potential bias appeared to be negligible since fine and gross locomotor activity (measured by infrared beam breakage) showed no difference during day or night noise exposure (Park et al. 2016).

The sensitivity to noise varies at different times of the day.

4.3.3.2 Involvement of Neurotrophic Signaling in the Differential Sensitivity to Noise Trauma Throughout the Day

A potential mechanism to explain the day and night differences in response to noise trauma included neurotrophic signaling in the cochlea (Meltser et al. 2014). Neurotrophins are important regulators of synaptogenesis and synaptic plasticity in the cochlea. Two important neutrophins, namely, neurotrophin-3 (NT-3) and brain-derived neurotrophic factor (BDNF), play an important role during cochlear development and in adult auditory recovery. Mice lacking NT-3 or BDNF, or their respective ligand-specific receptors of tropomyosin receptor kinase (TrkC or TrkB), lack a portion of the auditory neurons (Fritzsch et al. 2004). TrkC appears more important to auditory neuron development since its genetic ablation leads to the loss of 51–66% of auditory neurons, whereas loss of TrkB function causes a loss of only 15–20% of auditory neurons (from the high-frequency region). Their role appear inverted in the vestibular system where TrkB −/− mice show a loss of 56–85% of vestibular neurons whereas TrkC −/− only have 16–29% loss (Fritzsch et al. 2004). The similitude between the neurotrophin mutants and the receptor mutants provides strong evidence of their important contribution for the innervation in the inner ear.

The study from Meltser et al. revealed that the response of *Bdnf* transcription differed after day or night noise exposure. During the day, noise caused a 32-fold increase in *Bdnf* mRNA transcript levels, whereas no increase was after night noise. These findings indicate that the incapability of the cochlea to trigger a BDNF-dependent protective response after night noise could underlie the increased vulnerability to night noise exposure. Treatment before night noise exposure with dihydroxyflavone (DHF), a selective agonist of TrkB (Jang et al. 2010), restored the recovery of hearing thresholds to a level comparable to day noise exposure (in absence of drug treatment). Interestingly, night noise exposure caused a twofold reduction of the synaptic ribbons 2 weeks after noise exposure and DHF pretreatment protected synaptic ribbons (Meltser et al. 2014). These findings provide an evidence of the involvement of neurotrophins in the circadian recovery to noise trauma.

These results are somewhat conflicting with genetic studies that evaluated the contribution of NT-3 and BDNF to noise injury. In elegant genetic gain and loss of function studies, mice overexpressing Ntf3 or Bdnf via a tamoxifen-inducible Cre system (*Ntf3*^{STOP}*:Plp1/CreER*^{T} or *Bdnf*^{STOP}*:Plp1/CreER*^{T}) showed different responses to noise trauma, whereby only mice overexpressing *Ntf3* showed accelerated recovery—not those overexpressing *Bdnf* (Wan et al. 2014). A potential explanation for the differences between Meltser et al. and Wan et al. is that DHF treatment (that mimics Bdnf actions on TrkB) was acute (single injection) and performed at night, whereas the genetic model of Ntf3 overexpression is comparable to a constitutively active (chronic) TrkC system. The role of Ntf3 in the differential responses to day or night noise exposure remains to be investigated.

4.3.3.3 Molecular Biology of Cochlear Circadian Rhythm

The differential response to day or night noise trauma led to the hypothesis that the cochlea could harbor a clock machinery. Using a mouse reporter in which the

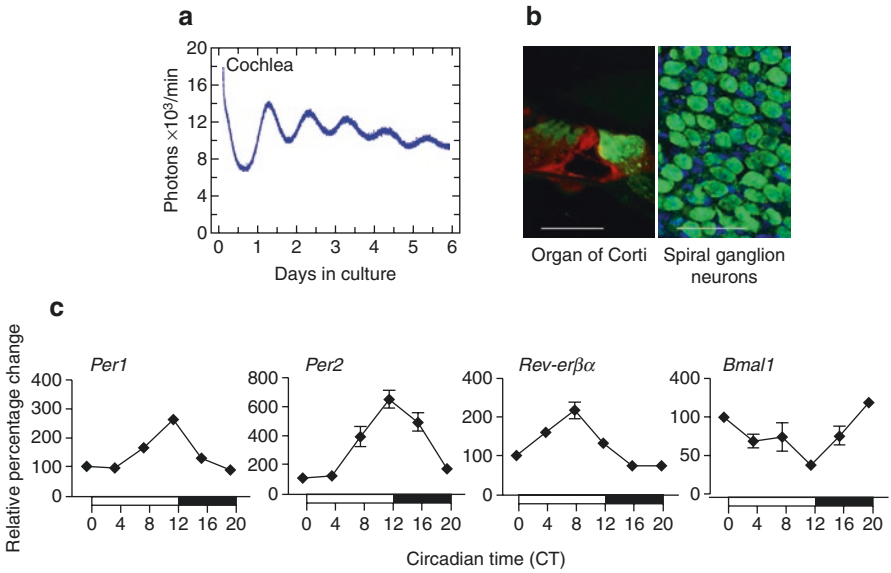

Fig. 4.4 Circadian oscillations in the cochlea: representative bioluminescence records of circadian PER2::LUC expression in cultured adult cochleae explants (**a**). (**b**) Immunostaining of PER2 in a cochlea of intact adult CBA/CaJ mouse shows the localization of the protein in inner and outer hair and supporting cells of the organ of Corti and in the spiral ganglion neurons of the cochlea. Scale bar: 50 mm. (**c**) Temporal expression of *Per1*, *Per2*, *Rev-Erβα*, and *Bmal1* mRNAs in the cochlea assessed by q-RTPCR. The *vertical axis* shows normalized mean values ± SEM (n = 3–4). The *horizontal axis* shows the sampling circadian time (CT) across 24 h at which the animals were sacrificed and samples collected. The *shaded area* illustrates the dark phase of the day from CT 12 to CT 0. All conditions were plotted as relative percentage change using CT 0 as baseline value. Basinou et al (2017)

luciferase gene was fused in frame with the endogenous *Period 2* gene (PER2::LUC) (Yoo et al. 2004), real-time bioluminescence from cochlear explants could be monitored as a readout of PER2 expression. PER2::LUC rhythms from the cochlea ex vivo appeared as ample as those from the liver (Fig. 4.4a), and after fading out, these rhythms could be kicked off with dexamethasone treatment, a known synchronizing agent (Meltser et al. 2014). PER2 protein expression originated from hair cells and spiral ganglion neurons (Fig. 4.4b).

The expression of core clock genes was further evidenced by qRT-PCR, thanks to improvements in a method of cochlear RNA extraction, yielding high quantities of RNA of a quality suitable for such molecular analyses (Vikhe Patil et al. 2015). Subsequently, the circadian expression of *Per1, Per2, Bmal1,* and *Rev-Erβα* was revealed, demonstrating that the cochlea harbors key components of the core clock machinery (Fig. 4.4c). Presence of additional circadian genes was revealed using a more sensitive methodology, namely, the NanoString nCounter (Cederroth and Canlon, unpublished observations).

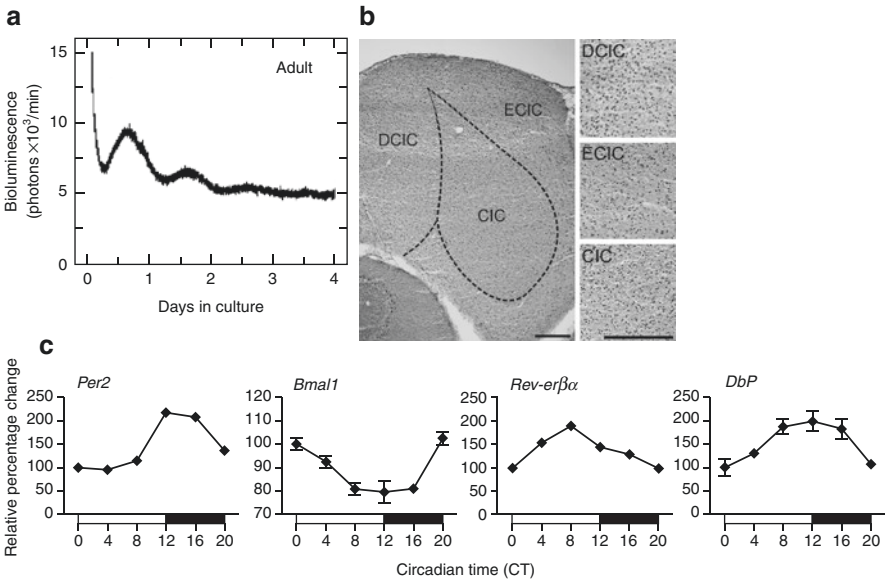

Fig. 4.5 Circadian oscillations in the IC. (**a**) Representative recordings of bioluminescence from whole IC at different ages (P4, P16, and adult) maintained in culture for 4 days. (**b**) Representative coronal section from the caudal part of the IC from a control animal sampled at ZT 11 showing PER2 immunoreactivity throughout the IC. The corresponding anteroposterior stereotaxic coordinate relative to the bregma is indicated in mm. The subdivisions of the different regions of the IC are outlined with the *dashed lines*. The *boxes* in each subdivision indicate the region of interest (DCIC, ECIC, and CIC) and are magnified in the inserts to the right. The *asterisk* and *daggers* indicate the aqueduct and cerebellum, respectively. Scale bars indicate 200 μm. (**c**) Temporal expression of clock mRNAs in the IC assessed with the NanoString nCounter. The *vertical axis* shows normalized mean values ± SEM (n = 3–4). The *horizontal axis* shows the sampling circadian time (CT) across 24 h at which the animals were sacrificed and samples collected. The *shaded area* illustrates the dark phase of the day from CT 12 to CT 0. All conditions were plotted as relative percentage change using CT 0 as baseline value. Modified from Park et al., J. Neuroscience, 2016, in press with permission from the Society of Neuroscience

The cochlea harbors key components of the core clock machinery.

Interestingly, noise exposure at night affected to a greater extent than day noise exposure the amplitude of *Per1, Per2, Bmal1,* and *Rev-Erβα* mRNA expression, a finding further validated via the monitoring of PER2::LUC rhythms in vitro. In addition, activation of TrkB with DHF modulated PER2::LUC oscillations to a greater extend in the day than in the night (Meltser et al. 2014). How these changes in cochlear rhythms are coupled to the physiological responses to noise trauma is a challenging area of research, but overall these findings illustrate the complex and interdependent links between noise, neurotrophins, and circadian rhythms in the cochlea.

4.3.3.4 Circadian Rhythms in the Inferior Colliculus

Recent experimental work from our laboratory revealed that the IC, an important relay of the auditory pathway involved in tinnitus, also possesses a molecular clock (Park et al. 2016). PER2::LUC rhythms in vitro were also captured in whole mount or sectioned IC (Fig. 4.5a). Immunohistochemistry revealed that PER2 is homogeneously expressed throughout the IC according to the different subdivisions, namely, the central nucleus of the IC (CIC), dorsal cortex of the IC (DIC), and external cortex of the IC (ECIC) along the rostro-caudal axis (Fig. 4.5b). NanoString nCounter arrays revealed circadian mRNA transcript profiles for *Per1, Per2,* and *Bmal1*, among others, and the clock-dependent genes *Dbp* (Fig. 4.5c). Curiously, the analysis of PER2::LUC rhythms indicates that the IC in the postnatal stage showed more robust circadian oscillations than the adult stage. In postnatal day 4 (P4) ICs, 100% of cultured IC oscillated, and in adult ones (P50), this dropped to 30%. To explain this phenomenon, multiple factors were investigated such as the experimenter, the gender of the animals, whole mount vs sections, the thickness of the sections, and their orientations (coronal, sagittal, horizontal), but none explained this decline in successful oscillations. A potential explanation is that aging influences the synchronicity of the oscillations, which suggests that a greater proportion of ICs might fail to show oscillations in adult stage, or that as an animal ages, components of the expression of core clock machinery could decrease until affecting the whole machinery.

Some scientists might argue that an oscillatory clock machinery might be detectable in any organ or tissue. However, as much as the clock machinery has been shown to be very important in the context of metabolic function such as hepatic glucose clearance and insulin secretion by the β-cells of the pancreas, that much it has been less obvious in the CNS. A landmark study investigated 27 areas of the brain and found that only 50% of these showed evidence of PER1 rhythmicity (Abe et al. 2002) indicating that the presence of the clock machinery cannot be expected everywhere. Similarly, results showing rhythms in reproductive organs have been conflicting (Dibner et al. 2010). Importantly, the physiological relevance of the clock system will only be revealed with functional studies using genetic mutants.

The presence of clock machinery cannot be expected everywhere.

In this regard, this information is still lacking for the cochlea and the IC. Nonetheless, the work of Park and colleagues revealed that clock genes in the IC also respond to noise, although in a partially inverted manner when compared to the cochlea. In the cochlea, night noise exposure affects the clock genes to a greater extent compared to day noise exposure. In contrast, day noise exposure alters clock genes in the IC more than the night noise exposure. These findings suggest that the response of the IC to noise is uncoupled to that of the cochlea. Supporting this idea, the induction of *Bdnf* transcription in the IC is similar between day and night noises, whereas in the cochlea, only day noise exposure triggers a *Bdnf* transcriptional response. Thus, the circadian relationship to noise sensitivity appears independent between the cochlea and the IC.

4.3.3.5 Central Influence of Cochlear and IC Rhythms: Predictive Models

The factors (*zeitgebers*) that synchronize cochlear or IC rhythms—if any—are still unknown. Several models can be proposed to predict the relationship between the cochlea, the IC, and the master clock (Fig. 4.6). It is possible that the cochlea or the IC function is fully dependent from SCN cues (directed control of auditory rhythms). However, the entrainment (the alignment of a circadian system's period and phase to the period and phase of an external rhythm) might not originate from the SCN but rather from other cues unrelated to SCN signals (e.g., feeding regimes), thus being completely independent from the master clock. Finally, a combination of the two models making the auditory system sensitive to some SCN-dependent or SCN-independent cues is what appears to be most plausible.

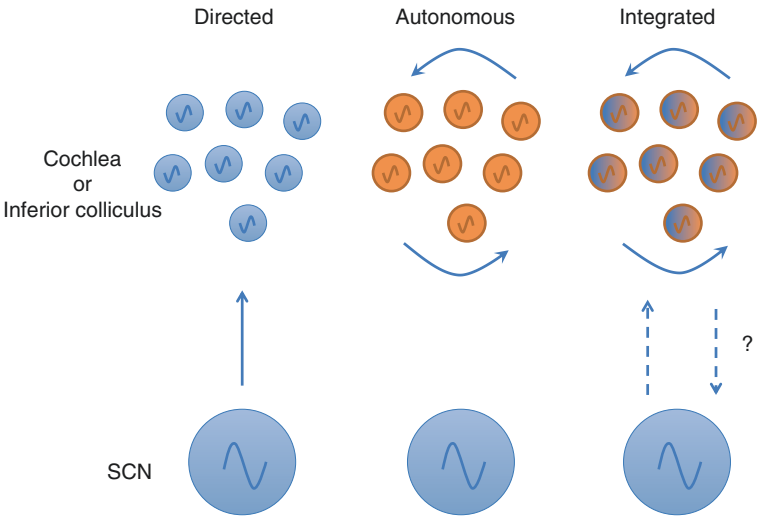

Fig. 4.6 Potential model of the circadian regulation of the auditory pathway. The SCN acts as the master clock that interacts with peripheral organs to synchronize their rhythms either directly or through the autonomic nervous system, feeding, or body temperature. Whether the SCN regulates the oscillations in the auditory circuit or whether cells from the cochlea or the IC are completely autonomous remains to be determined. A plausible mechanism is an integrated system whereby the cochlea and the IC have some control over their rhythms, coordinated by either direct or indirect inputs from the SCN. *Blue circles* represent SCN-driven oscillators, and *orange circles* represent autonomous oscillators. *Solid arrows* represent direct input, whereas *dashed arrows* represent an influence over the oscillators. Whether the cochlea or the IC communicates back to the SCN is unknown and illustrated with a question mark (?). Modified from Gerstner et al., Nature Reviews Neuroscience, 2010, 11:577 with permission from the Nature Publishing Group

4.3.4 Auditory Pathologies and Disrupted Circadian Rhythms

Whether there is a relationship between circadian rhythms and tinnitus remains unknown. The IC has been implicated in auditory pathologies such as tinnitus, hyperacusis, and seizures. In rats, direct stimulation of the IC increases the susceptibility to audiogenic seizures (Faingold et al. 1992).

Audiogenic seizures are convulsions induced by extended exposure to high-frequency sound, particularly in small mammals.

When generated at night, audiogenic seizures induced by sound stimulation cause greater convulsions and death in comparison to day stimulation (Halberg et al. 1958). These two studies connect the inferior colliculus with the circadian vulnerability to audiogenic seizures. Interestingly, mice lacking the clock-controlled genes encoding three PAR bZip (proline and acidic amino-acid-rich basic leucine zipper) proteins (*Tef*, *Hlf*, and *Dbp*) also develop spontaneous seizures and are more vulnerable to audiogenic seizures (Gachon et al. 2004b). Curiously, *Tef* and *Hlf* do not show circadian expression in the IC (Park et al. 2016), which might indicate that the source of audiogenic seizures in this triple mutant might not stem from the IC but rather in the cochlea, where these transcription factors were found highly circadian (Cederroth and Canlon, unpublished observations). It is also possible that other parts of the auditory pathway show strong circadian rhythms; however, this requires further investigation.

Assuming that disruption of circadian rhythms in the cochlea could not only be related to central auditory pathologies such as seizures but also to tinnitus and hyperacusis, then important CNS-related phenotypes should be expected in mutants in which the clock machinery has been specifically knocked out from the cochlea. Unfortunately, to the best of our knowledge, there is no genetic tool to allow cochlea-specific deletion of clock-related gene function without affecting other central auditory and non-auditory areas or other peripheral organs involved in circadian rhythms. Thus, testing this hypothesis will remain a challenging task. Nonetheless, studies have found in animal models of noise-induced tinnitus that the development of tinnitus correlates with a greater number of missing synaptic ribbons in inner hair cells, leading to decreased wave I amplitude of the ABR (Ruttiger et al. 2013). The permanent damage occurring after night noise trauma suggests greater loss of ribbons than after day noise trauma, although this remains to be ascertained. DPOAE measures should also clarify whether outer hair cell dysfunction contributes to the permanent threshold shifts happening after night noise exposure. The relevance of these findings to humans was evidenced in a study from Schaette et al. in which tinnitus subjects displayed lower wave I amplitude of click ABRs than control subjects (Schaette and McAlpine 2011). Further research is required to reveal the importance of cochlear rhythms in the generation of auditory pathologies.

In the animal models of noise-induced tinnitus, the development of tinnitus correlated with a greater number of missing synaptic ribbons in inner hair cells, leading to a decreased amplitude of the ABR wave I.

Importantly, no information is available on whether disruption of circadian rhythms causes auditory dysfunctions or tinnitus in humans. Epidemiological studies on shift workers, flight crews, and others will need to investigate whether the timing of noise exposure combined with the working schedule are associated with hearing deficits or tinnitus.

4.3.4.1 Psychological Consequences of Disrupted Circadian Rhythms and the Potential Role in Tinnitus

While the causal relationship between stress, depression, and anxiety in tinnitus is still unclear, there is an evident association of these emotional factors with tinnitus (see Chap. 3). Since these psychological states are controlled by circadian rhythms, it is tempting to speculate that disruptions in daily rhythms may increase the vulnerability to develop tinnitus in association with a psychological burden or increase the severity of an already established tinnitus symptom.

Disruptions in daily rhythms may possibly increase the vulnerability to develop tinnitus in association with a psychological burden.

Animal studies support the notion that the disruption of the clock system causes depression and anxiety. Mice harboring a point mutation in the *Clock* gene are hyperactive over the light-dark cycle and display reduced depression-like behavior and increased reward value (Dzirasa et al. 2010; McClung et al. 2005; Roybal et al. 2007). Dopamine release is increased in *Clock* mutants, and sensitivity to dopamine receptor agonist is increased (Spencer et al. 2012). Mice lacking *Per1* and *Per2* display increased anxiety (Spencer et al. 2013). In people with major depressive disorder, the amplitude and rhythm of melatonin secretion is altered. It has been proposed that neuropsychiatric disorders are the result of desynchrony between key behavioral and physiological events, as it is the case for major depression (e.g., different sleep-wake cycles, cognition, mood, hormonal, immune, metabolic, and thermoregulatory) (Germain and Kupfer 2008). This is why many studies do not assess absolute changes in serum levels of key hormones but rather investigate the deviations from normal circadian patterns.

Psychosocial stress at different times of the day can alter the molecular clock.

Reversely, psychosocial stress at different times of the day can alter the molecular clock. Repeated social defeat at night but not in the day blunts activity rhythms and flattens glucocorticoid rhythms (Bartlang et al. 2012). At the molecular level, this phenomenon was associated with increased amplitude of PER2::LUC rhythms in the SCN after night social defeat and in the adrenal gland after day social defeat (Bartlang et al. 2014). Since the SCN does not express GR (Balsalobre et al. 2000), it is thought that either indirect feedback from circulating glucocorticoids acting on other brain areas expressing GRs could occur or that glucocorticoid action on the raphe nucleus could reach the SCN via serotonergic projections (Kiessling et al. 2010; Malek et al. 2007). Another paradigm using chronic stress but being unpredictable causes a decrease in PER2 protein expression in the SCN (Jiang et al. 2011). Thus, different stressors act differently on the molecular clock and its alterations, whatever the direction (either suppressed or increased rhythmicity) could lead to changes in physiological functions such as the amplitude of glucocorticoid secretion. The presence of GR receptors in the cochlea (see Chap. 2) and the known effects of stress on the auditory system (Meltser and Canlon 2011; Tahera et al. 2006) suggests that tinnitus generation by stress (*stress inducing tinnitus*) may occur at the level of the cochlea. On the other hand, the exacerbation of tinnitus severity by stress (*stress increasing tinnitus*) may occur through the known involvement of the limbic system in tinnitus (see Chap. 3) (Elgoyhen et al. 2015).

4.4 Clinical Implications of Circadian Influences for Tinnitus Therapy

Although auditory chronobiology is an extremely new discipline of research, it draws the attention to the important association of diurnal rhythms with hearing. The key discovery of the increased vulnerability of the rodent auditory system to noise at night in comparison to daytime helps to better understand the increased incidence of hearing loss in communities exposed to 24 h of noise pollution (aircraft, train, or highway noise) (Basner et al. 2014, 2015).

Understanding the pathological basis of tinnitus (such as night noise-induced hearing loss) is one issue in which the circadian rhythms may be very helpful. Another issue is the use of this new knowledge for therapeutic purposes. The physiological rhythmicity of cells, tissues, and organs keeps our bodies in the state of homeostasis and health. Disrupting this rhythm can have pathological consequences, and it remains to be determined whether it can be corrected. Daily routines (also known as social rhythm) such as going to work or school or exercise influence the sleep patterns, and correlations have been found between people with daily routines and healthy sleep (Moss et al. 2015).

To recover from disturbed routines, a special treatment has been developed, namely, social rhythm therapy (Haynes et al. 2016a). Social rhythm therapy is an evidence-based psychotherapy and has been used for various mood conditions,

such as bipolar disorder, post-traumatic stress disorder, insomnia, and depression (Haynes 2015; Haynes et al. 2016a, b). However, the effectiveness of social rhythm therapy has not been studied, to our knowledge, in individuals with tinnitus. Nevertheless, it could be an attractive therapeutic avenue for patients with tinnitus, since near 50% of them have at least one comorbid psychological disorder (see Chap. 6). The question remains whether reinstating daily routines would restore diurnal rhythms and have a positive influence on tinnitus or on hearing abilities in general.

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