The Circadian Control of Sleep

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Abstract The sleep/wake cycle is arguably the most familiar output of the circadian system, however, sleep is a complex biological process that arises from multiple brain regions and neurotransmitters, which is regulated by numerous physiological and environmental factors. These include a circadian drive for wakefulness as well as an increase in the requirement for sleep with prolonged waking (the sleep homeostat). In this chapter, we describe the regulation of sleep, with a particular emphasis on the contribution of the circadian system. Since their identification, the role of clock genes in the regulation of sleep has attracted considerable interest, and here, we provide an overview of the interplay between specific elements of the molecular clock with the sleep regulatory system. Finally, we summarise the role of the light environment, melatonin and social cues in the modulation of sleep, with a focus on the role of melanopsin ganglion cells.

Keywords Sleep • Circadian • Clock gene • Melatonin • Melanopsin

1 Introduction

The regular cycle of sleep and wakefulness is perhaps the most obvious 24-h oscillation. However, sleep is a complex physiological process involving the interaction of multiple neurotransmitter systems and a diverse network of mutually inhibiting arousal and sleep-promoting neurons. This highly coordinated neural

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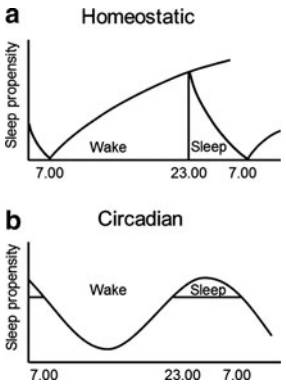

Fig. 1 Sleep regulation by homeostatic and circadian mechanisms. (**a**) The homeostatic drive for sleep increases sleep propensity with prolonged wakefulness. Sleep pressure declines following sleep, but increases again at waking. (**b**) Circadian drive. The circadian regulation of sleep creates a drive for wakefulness during the day, which declines at night. As such, sleep propensity is low during the day, but increases at night. Figure based on that of Borbely (1982)

activity drives alternating patterns of behaviour characterised by changes in rest/activity, body posture and responsiveness to stimuli (Tobler 1995). Reflecting the complexity of the neurobiological processes involved, sleep is regulated by a range of internal and external drivers. In this chapter, we will discuss these parameters, with a particular focus on the contribution of the circadian clock and its interaction with the sleep/wake regulatory system.

The primary measures used to define sleep in mammals are the electroencephalogram (EEG) and electromyogram (EMG) which are used to characterise sleep as either rapid eye movement (REM) or non-rapid eye movement (NREM) states. This gold standard approach of classifying sleep not only enables the assessment of sleep structure but also permits power spectral analysis of the EEG for different sleep/wake states. In 1982, Borbely proposed the 'two process model' of sleep regulation which provides a conceptual framework for understanding the timing and structure of sleep/wake behaviour. It describes a homeostatic process (S), which increases as a function of the duration of wakefulness and a circadian process (C), determining the timing of sleep and wakefulness (Borbely 1982) (Fig. 1). In humans the consolidation of wakefulness into a single bout is a result of the phase relationship between these two processes where the circadian drive for arousal opposes the increasing propensity to sleep across the day (Dijk and Czeisler 1995). There has been considerable progress in our understanding of the circadian process with the anatomical location of the master circadian pacemaker identified within the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. However, relatively less is known regarding the molecular and cellular processes underlying sleep homeostasis and its interaction with the circadian timing system.

2 Homeostatic Regulation of Sleep

The homeostatic process regulates the propensity for sleep, which increases exponentially at the onset of wakefulness and subsequently diminishes during sleep (Fig. 1a). It is functionally distinct from the circadian system since rodents with lesions of the SCN continue to exhibit a strong compensatory increase in sleep after total sleep deprivation (Mistlberger et al. 1983; Tobler et al. 1983). The best characterised marker of sleep homeostasis and a correlate of sleep intensity is EEG slow-wave activity (SWA, 0.5–4 Hz) during NREM sleep which increases as a function of the duration of prior wakefulness and declines exponentially across a typical sleep episode (Borbely et al. 1981; Lancel et al. 1991). It has been suggested that this homeostatic decrease in SWA during sleep is associated with a downscaling of synaptic strength and is important for the positive effects of sleep on neural function (Tononi and Cirelli 2006). EEG power in the theta frequency range (5–7 Hz) has also been identified to reflect sleep propensity during quiet wakefulness. Notably studies in both rodents and humans have demonstrated that a rise in EEG theta power during enforced wakefulness was able to predict the increase in EEG SWA during subsequent sleep (Finelli et al. 2000; Vyazovskiy and Tobler 2005). It is now appreciated that EEG SWA is topographically represented in the cortex with changes in SWA occurring in restricted brain regions with different temporal dynamics (Rusterholz and Achermann 2011; Zavada et al. 2009) which have been associated with alterations in learning and performance (Huber et al. 2004, 2006; Murphy et al. 2011). Importantly this provides evidence that the regulation of SWA and sleep homeostasis can occur at a local level. A recent study has further reinforced this concept of 'local' sleep regulation after identifying discrete cortical regions of the rat brain that effectively go 'offline' during a period of prolonged wakefulness even though the animal remains awake by the assessment of global EEG parameters (Vyazovskiy et al. 2011).

Identifying a neuroanatomical basis of homeostatic sleep regulation has been extremely challenging and remains one of the outstanding questions in sleep research. Sleep-promoting neurons have been previously identified in the ventrolateral preoptic area (VLPO) and median preoptic nucleus (MnPO) of the hypothalamus (Gong et al. 2004; Sherin et al. 1996); however, the recent discovery of a population of sleep-active neurons in the cortex has further supported an anatomical basis of homeostatic sleep regulation (Gerashchenko et al. 2008; Pasumarthi et al. 2010). These sleep-active cells expressing neuronal nitric oxide synthase are a subpopulation of GABAergic interneurons that project long distances throughout the cerebral cortex with the number of cells activated during sleep proportional to SWA intensity (Gerashchenko et al. 2008). Determining the neuronal circuitry and mechanisms that result in the activation of these cells during sleep will further increase our understanding of their potential role in homeostatic sleep regulation.

Research has also focused on the role of chemical mediators in the regulation of sleep homeostasis. Such a mediator would be expected to accumulate after prolonged wakefulness or sleep deprivation and decline during sleep. Several

candidate substances have been proposed but particular focus has been placed on the purine nucleoside adenosine (Basheer et al. 2004). Microdialysis studies in cats have demonstrated that adenosine selectively increases in the basal forebrain (BF) during 6 h of sleep deprivation (Porkka-Heiskanen et al. 1997, 2000). Furthermore, perfusion of adenosine into the BF of freely moving cats reduces wakefulness, decreases cortical arousal (Portas et al. 1997) and activates neurons in the VLPO (Scammell et al. 2001). A study employing a significantly longer period of sleep deprivation (11 h) has shown that initially nitric oxide followed by adenosine accumulates in the BF, with levels of these molecules increasing in the frontal cortex several hours later, providing further insight into the temporal dynamics of sleep homeostasis (Kalinchuk et al. 2011). Caffeine, a potent stimulant, functions as an adenosine antagonist at both A_1 and A_2 receptors. Studies involving knockout mice for these receptors indicate that blockade of the A_2 receptor mediates these wake-promoting effects since caffeine could promote arousal in wild-type and A_1 knockout mice but not in mice deficient in the A_{2A} receptor (Huang et al. 2005). In addition, caffeine administered to young male subjects during sleep deprivation reduced subjective sleepiness and EEG theta activity and decreased SWA during subsequent recovery sleep (Landolt 2004). This ability of caffeine to reduce the accumulation of sleep propensity after prolonged wakefulness further proposes a critical role of adenosine in sleep homeostasis. Prostaglandin D_2 (PGD_2), has also been identified as a putative endogenous sleep-promoting factor (Huang et al. 2007), and evidence suggests it may also mediate its effects on sleep through A_{2A} receptors (Satoh et al. 1996).

3 Circadian Regulation of Sleep

The circadian influence on sleep was soon appreciated after it was demonstrated that rhythms of sleep and wakefulness persist in free-running conditions and are strongly synchronised to the rhythm of core body temperature (Czeisler et al. 1980). The circadian regulation of sleep is independent of prior wakefulness and determines the phases of high and low sleep propensity across the 24-h day (Fig. 1b; Borbely and Achermann 1999). Studies in humans using forced desynchrony protocols (enforced 28-h sleep/wake cycles) have revealed the uncoupling of the sleep/wake cycle from endogenous circadian processes and further support the dualistic view of the control of sleep (Dijk and Lockley 2002). Human volunteers scheduled to a 28-h rest/activity cycle were only able to sleep undisturbed for an 8-h period when sleep initiation occurred 6 h before the endogenous circadian temperature minimum (Dijk and Czeisler 1994). Evidence strongly suggests that the circadian process arises from the SCN located in the anterior hypothalamus (Weaver 1998). In rodents, targeted lesioning of the SCN disrupts circadian rhythms in locomotor activity, feeding and drinking (Stephan and Zucker 1972; Moore 1983), whilst surgically implanted SCN tissue grafts can restore rhythms with a period determined by the donor, not the recipient (Ralph et al. 1990; King et al. 2003).

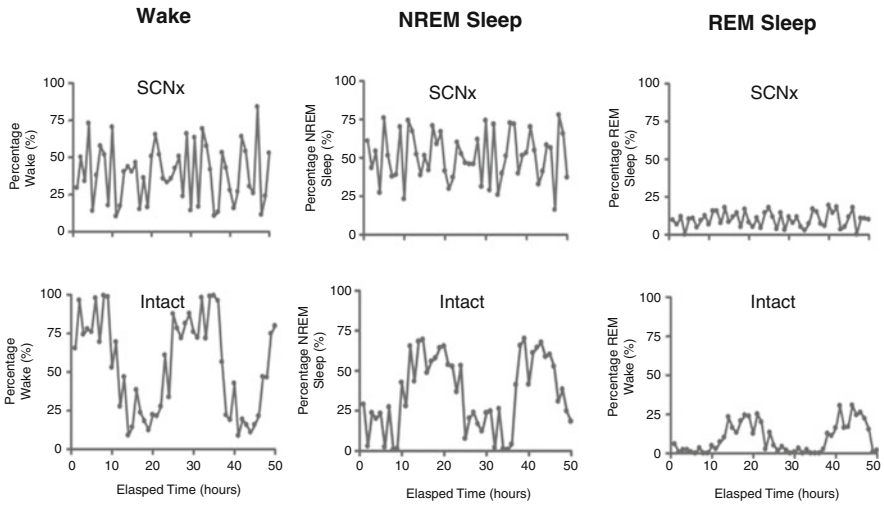

Fig. 2 Circadian rhythms in wakefulness, NREM and REM sleep are abolished in SCN-lesioned rats. Wakefulness, NREM and REM sleep plotted for 50 consecutive hours in constant darkness for an individual SCN-lesioned rat (SCNx, *top panels*) and a rat with an intact SCN (*bottom panels*). Data points represent hourly percentage values for an individual rat (Figure based on unpublished data, S. Fisher)

These transplantation studies were essential in confirming the SCN as the principal mammalian timekeeping structure. Through a number of intermediate relay nuclei, the SCN innervates multiple brain areas involved in sleep/wake cycle regulation including the VLPO and the MnPO areas (Deurveilher and Semba 2005). The SCN is known to receive information relating to the specific sleep/wake states, as SCN electrical firing is modified by changes in vigilance state in the rat (Deboer et al. 2003). Neuronal activity in the SCN was lowered during NREM sleep and by contrast was increased when the rat entered periods of REM sleep independent of circadian phase (Deboer et al. 2003). Furthermore, after prolonged sleep deprivation (6 h), the circadian amplitude of SCN electrical activity was reported to be suppressed during recovery sleep, an effect persisting for up to 7 h (Deboer et al. 2007). This suggests that sleep deprivation directly modulates the electrical rhythm of the circadian clock in addition to its well-characterised effects on the sleep homeostat.

Lesions of the SCN in rodents also leads to a disruption and flattening of the rhythm of sleep and wakefulness, where animals no longer display consolidated episodes of NREM and REM sleep and instead exhibit numerous transitions between states together with frequent arousals (Fig. 2). The ‘opponent process’ model proposed by Edgar and colleagues specifies that the circadian process actively promotes the initiation and maintenance of wakefulness opposing the homeostatic drive for sleep (Edgar et al. 1993). This hypothesis is primarily based on SCN lesion studies performed in squirrel monkeys which results in an increase in total sleep time compared to sham-operated controls (Edgar et al. 1993).

Similar observations have been made in mice where SCN lesions increase sleep time by ~8.1 % (Easton et al. 2004), suggesting a wider role for the SCN in sleep regulation beyond purely the timing of vigilance states. By contrast, the majority of SCN lesion studies performed in rats do not result in major changes in the total amount of sleep (Eastman et al. 1984; Mistlberger et al. 1987; Mouret et al. 1978), and homeostatic regulation of sleep is also preserved in arrhythmic hamsters (Larkin et al. 2004). This apparent controversy may suggest that the SCN has both a wake- and sleep-promoting action, promoting arousal at one time of the day and sleep at a different time, possibly by changing the balance of its output signal (Dijk and Duffy 1999; Mistlberger et al. 1983).

3.1 Clock Genes and Sleep

The important role that clock genes play in the generation of circadian rhythms is well established. Over the last 20 years, there has been remarkable progress in our understanding of the molecular mechanisms responsible for generating the cell-autonomous oscillations which make up the circadian system. This autoregulatory network relies on the interaction between both positive and negative transcriptional/translational feedback loops. In mammals, the transcription factors CLOCK and BMAL1 form a heterodimeric complex which drives the transcription of the *Period* (*Per 1*, *2*, *3*) and *Cryptochrome* (*Cry1*, *2*) genes through binding to E-box promoter sequences (CACGTG) (Gekakis et al. 1998). Additionally, the transcription factor neuronal PAS domain protein 2 (NPAS2), an analogue of CLOCK, is expressed in the forebrain nuclei, basal ganglia and limbic system (Garcia et al. 2000). NPAS2 can also heterodimerise with BMAL1 to activate the transcription of *Per* and *Cry* genes (Reick et al. 2001). Whilst it was originally suggested that NPAS2 is not found in the SCN (Garcia et al. 2000), later studies showed that it is both expressed in the SCN and can functionally substitute for CLOCK (DeBruyne et al. 2007). PER and CRY proteins are synthesised in the cytoplasm and form complexes that are phosphorylated by casein kinases I δ and ε which subsequently re-enter the nucleus and bind to CLOCK/NPAS2:BMAL1 heterodimers to inhibit their own transcription (Reppert and Weaver 2002). Formation of CLOCK/BMAL1 heterodimers can also result in the activation of the retinoic acid-related orphan nuclear receptors Rora and Rev-erbα. Rev-erbα can inhibit CLOCK and BMAL1 expression, whilst by contrast, RORA is an activator which functions to reinforce oscillations and increase levels of *Bmal1* in the absence of PER and CRY proteins (Buhr and Takahashi 2013; O'Neill et al. 2013). In the mammalian circadian clock, a certain degree of overlap exists as single mutations in the clock genes *Per* and *Cry* do not result in arrhythmicity (Bae et al. 2001; Okamura et al. 1999). Additionally, in mice *Per3* is not required for circadian rhythm generation with only minor effects on circadian period reported in its absence (Shearman et al. 2000).

Studies involving clock gene mutant mice have allowed a finer dissection of the role of individual clock components in circadian rhythm generation but have also

shed new light on their potential role in the regulation of sleep. The advantage of using genetic approaches to disrupt the circadian system are that SCN neuronal connections remain largely intact; however, developmental effects of the gene knockout cannot be excluded. Below, we summarise the role of specific clock genes and clock-controlled genes in the regulation of sleep, including their effects on the total amount of sleep, sleep structure and the EEG. These data are summarised in Table 1.

3.1.1 *Cryptochrome*

Cry1 and *Cry2* double-knockout mice ($Cry1,2^{-/-}$) are rhythmic under a regular light/dark cycle but arrhythmic under constant conditions (van der Horst et al. 1999; Vitaterna et al. 1999). Cyclic expression of the *Per* genes is eliminated in both the SCN and peripheral tissues in these mice (Okamura et al. 1999), although they display normal masking responses to light (Mrosovsky 2001). In addition, $Cry1,2^{-/-}$ mice generated on the C3H melatonin-proficient background fail to show a circadian rhythm in melatonin production, one of the most reliable output measures of the circadian clock (Yamanaka et al. 2010). However, independent of whether they display rhythmicity, $Cry1,2^{-/-}$ mice exhibit a 1.8-h increase in NREM sleep with an approximate 40 % increase in NREM sleep bout duration (Wisor et al. 2002). Furthermore, they show an elevation of EEG SWA during baseline recordings and after sleep deprivation, indicating that the absence of both *Cry* genes leads to increases in the accumulation of sleep pressure. $Cry1,2^{-/-}$ mice also fail to show the typical compensatory rebound in NREM sleep after enforced wakefulness (Wisor et al. 2002). This sleep phenotype cannot be ascribed to either of the *Cry* genes alone since it is not replicated in single *Cry* knockout mice (Wisor et al. 2008). The $Cry1,2^{-/-}$ mouse phenotype appears to be more complex than simply a genetic model of arrhythmia and actually implicates a larger role for *Cry* genes in the homeostatic sleep regulation.

3.1.2 *Period*

Mice with mutations in both *Per1* and *Per2* ($Per1,2^{-/-}$) genes exhibit robust diurnal rhythms only under a standard light/dark cycle. In contrast to $Cry1,2^{-/-}$ mice, they show no change in the total amount of sleep across a 24-h period under a regular L:D cycle (Kopp et al. 2002) or under constant darkness (Shiromani et al. 2004). Similarly EEG recordings performed in single mutant *Per1* and *Per2* mice did not find any alteration in total sleep time and demonstrated that they have a normal homeostatic response to sleep deprivation (Kopp et al. 2002). After sleep deprivation, $Per1,2^{-/-}$ mice exhibit the expected increase in EEG SWA in NREM sleep, suggesting the homeostatic control of sleep is intact. A more recent study using Per3 knockout mice ($Per3^{-/-}$) on the C57BL/6J background identified differences in the temporal distribution of sleep with an increase in NREM and REM sleep immediately after the dark/light transition (Hasan et al. 2011). This is

Table 1 Summary of sleep phenotype of clock gene mutant/knockout models

	Total sleep (24 h)						
Gene	LD	DD	Baseline EEG	REM/NREM	Sleep deprivation	Other effects	References
Cry1/2$^{-/-}$	1.8 h ↑ in NREM	1.5 h ↑ in NREM	NREM delta power ↑	Attenuated sleep/wake rhythm across LD cycle	Compensatory response to sleep loss ↓	NREM bout duration ↑	Wisor et al. (2002)
Per1/2$^{ldc/ldc}$	No effect	No effect	No effect on NREM delta or REM theta power	Wake time in L ↑	Compensatory response to sleep loss	Longer wake bouts in D Temperature in D period ↓	Shiromani et al. (2004)
Bmal1$^{-/-}$	1.5 h ↑ in total sleep	6.2 % ↑ in NREM	NREM delta power ↑ Flattened distribution of EEG delta power	Arrhythmic sleep/wake states in DD	REM sleep rebound ↓	↑ body temperature at L–D transition absent Sleep fragmentation ↑	Laposky et al. (2005)
Clock^{m1Jt}	2 h ↓ in total sleep	1 h to 2 h ↓ in NREM	Total NREM delta energy in 24-h baseline ↓ No effect on NREM delta power No effect on in EEG theta or sigma power	NREM sleep in L ↓	Compensatory response to sleep loss REM sleep rebound ↓	NREM/REM sleep onset latency ↓ NREM bout duration ↓ Obesity, metabolic syndrome, diabetes	Naylor et al. (2000) Turek et al. (2005) Marcheva et al. (2010)
Npas2$^{-/-}$	~40 min ↓ in NREM		Activity in spindle frequency ↓ Shift of NREM delta power to faster frequency	Wake time in D phase ↑ NREM/REM in D phase ↓	Compensatory response to sleep loss ↓ (*male mice only*)		Dudley et al. (2003), Franken et al. (2006)
Dec2^{P385R}			No effect on NREM delta or REM theta power	NREM/REM in L phase ↓	Compensatory response to sleep loss ↓	NREM episodes in L ↑ Sleep fragmentation ↑	He et al. (2009)

PK2$^{-/-}$	1.3 h ↓ total sleep	1.3 h ↓ total sleep	EEG theta power ↓ in REM	REM sleep duration ↑	Compensatory response to sleep loss ↓	NREM/REM sleep onset latency ↓ Less responsive to environmental arousal	Hu et al. (2007)
Dbp$^{-/-}$	No effect	No effect	Amplitude of delta power ↓ NREM delta power ↓ in D period Theta frequency peak in REM sleep ↑	Sleep during L ↓ Sleep during D ↑ Circadian amplitude of the sleep distribution ↓	Compensatory response to sleep loss REM sleep rebound absent	Greater disruption in DD than under LD and ↓ sleep amplitude	Franken et al. (2000)
Vipr2$^{-/-}$	~50 min ↑ in NREM	No effect	Normal EEG delta power in NREM sleep	Less defined sleep and wake phases in D and L		Sleep/wake transitions and brief arousals ↑ Ultradian cycles of sleep/wake in DD	Sheward et al. (2010)
Per3	No effect	No effect	Temporal distribution of sleep altered EEG delta power in D period ↑ Theta frequency peak in REM sleep ↓	NREM/REM after D–L transition ↑	Accumulation of EEG delta power ↑ in recovery sleep Number of NREM sleep bouts ↑	Running-wheel activity ↑ in D	Shiromani et al. (2004) Hasan et al. (2011)

L stands for Light
D stands for Dark

suggestive of an enhanced response to the sleep-promoting effects of light; however, this appears to be in contrast to the effects of light on running-wheel activity in *Per3*$^{-/-}$ mice, where a reduction in negative masking and a shorter free-running period under constant light were reported (van der Veen and Archer 2010). *Per3*$^{-/-}$ mice show enhanced accumulation of EEG delta power across the active period (Hasan et al. 2011). This increased sleep pressure in *Per3*$^{-/-}$ mice may explain the increase in sleep observed early in the light period. *Per* gene expression can also be modulated through manipulations of homeostatic sleep pressure with an elevation of *Per1* and *Per2* in the cortex detected after sleep deprivation (Wisor et al. 2002). Additionally, studies in humans have linked functional polymorphisms in the *Per3* gene to differences in sleep homeostasis in terms of EEG SWA in NREM sleep but also in theta and alpha frequencies during wakefulness and REM sleep (Viola et al. 2007). A polymorphism in the promoter region of *Per3* has been recently associated with delayed sleep-phase syndrome, a situation where sleep/wake timing of the individual is delayed relative to the external light/dark cycle (Archer et al. 2010). Overall evidence suggests that unlike the *Cry* genes, *Per1* and *Per2* are not implicated in homeostatic sleep regulation, but indicate an emerging role for *Per3* in sleep homeostasis.

3.1.3 *Bmal1*

Both *Cry* and *Per* gene expression are under the control of CLOCK/NPAS2 and BMAL1 heterodimers. Mutations in these genes indicate they are important in regulating circadian function but interestingly also impact the underlying sleep phenotype. *Bmal1*$^{-/-}$ mice are arrhythmic and exhibit decreased activity levels when kept under a regular light/dark cycle or constant conditions (Bunger et al. 2000). These mice exhibit a 1.5-h increase in total sleep predominantly due to an increase in NREM and REM sleep during the active phase (Laposky et al. 2005). *Bmal1*$^{-/-}$ mice also failed to show the predictable increase in arousal or body temperature during the light/dark transition, indicating potential defects in light input pathways to the SCN. Sleep was highly fragmented in these animals with an increase in the number of sleep bouts during the light period. They also lacked a rhythm in sleep propensity, as indicated by the flattened distribution of EEG delta power in NREM sleep, which was also elevated under baseline conditions indicating they function under a high level of sleep pressure. However, the REM sleep rebound after sleep deprivation was attenuated in *Bmal1*$^{-/-}$ mice. This modulation of both sleep amount and intensity in *Bmal1* mutant mice suggests a role for this clock gene in the homeostatic regulation of sleep.

3.1.4 *Clock*

A mutagenesis screen performed by Joseph Takahashi and colleagues led to the discovery of *Clock*, the first mammalian gene identified to be important for normal circadian function (Vitaterna et al. 1994). A dominant negative mutation of this

gene resulted in a lengthening of circadian period and arrhythmicity in homozygous *Clock* mutants under free-running conditions but not under a regular L:D cycle (Vitaterna et al. 1994). In mice heterozygous and homozygous for the *Clock* mutation, total sleep time was decreased by 1 and 2 h, respectively, compared to wild-type animals (Naylor et al. 2000). NREM sleep bout duration was also significantly reduced in *Clock* homozygous mice, although EEG delta power in NREM sleep remained unaffected, indicating that the decrease in the length of sleep was not compensated by changes in sleep intensity (Naylor et al. 2000). Additionally, these animals showed a normal rebound in sleep after 6 h sleep deprivation. This infers the *Clock* gene is important in regulating sleep amount and timing but is not critical for the functioning of all aspects of homeostatic sleep regulation. Furthermore, it should be noted that *Clock*-mutant animals display a complex phenotype, including obesity, metabolic syndrome (Turek et al. 2005) and diabetes (Marcheva et al. 2010) which may also impact changes in the sleep/wake cycle. The central role of CLOCK in the circadian oscillator was challenged when it was shown that in contrast to *Clock* mutants, $Clock^{-/-}$ mice show robust circadian rhythms of locomotor activity (Debruyne et al. 2006). However, this may be explained by the functional substitution of NPAS2 compensating in *Clock* knockouts (see below).

3.1.5 Other Canonical Clock Genes

NPAS2, an analogue of *Clock*, is a basic helix–loop–helix PAS domain transcription factor. It forms a heterodimeric complex with BMAL1 leading to the transcription of the negative regulators *Cry* and *Per*. NPAS2 is expressed in the forebrain nuclei, basal ganglia and limbic system (Garcia et al. 2000), as well as the SCN where it can substitute for CLOCK (DeBruyne et al. 2007). This substitution of NPAS2 for CLOCK is likely to account for the difference in phenotype between *Clock*-mutant and knockout mice (Debruyne et al. 2006). Wheel-running studies performed in $Npas2^{-/-}$ mice demonstrate a reduction in the free-running period, increases in the rates of re-entrainment and attenuation of the typical 'rest phase' in the second half of the dark period (Dudley et al. 2003). The authors confirmed the latter observation using EEG recordings demonstrating that $Npas2^{-/-}$ mice remained awake for a greater proportion of the dark period with reductions in NREM and REM sleep. These mice also display a reduction in the amount of recovery sleep following sleep deprivation, a difference that was only apparent in male $Npas2^{-/-}$ mice (Franken et al. 2006). These mice also show changes in the EEG during NREM sleep, with a reduction in activity in the spindle frequency range (10–15 Hz) and a shift of delta activity towards faster frequencies, signifying a role for NPAS2 in the propagation of EEG oscillations (Franken et al. 2006). To date, no study has investigated sleep in $Clock^{-/-}$ or *Clock/Npas2* double-knockout mice.

The basic helix–loop–helix transcription factors *Dec1* (Sharp2) and *Dec2* (Sharp1) are expressed in a circadian manner in the SCN and are important regulatory components of the molecular clock. They act primarily as negative

modulators which repress CLOCK/BMAL-induced gene expression of the Per1 promoter (Honma et al. 2002). Studies in mice deficient in *Dec1* and *Dec2* indicate a role for these transcription factors in the control of period length, phase resetting and circadian entrainment (Rossner et al. 2008). A point mutation in *Dec2* has been associated with a short sleep phenotype in humans (He et al. 2009). The small sample size in this study led the investigators to test this linkage by replicating the $DEC2^{P385R}$ mutation in a murine model. They were convincingly able to reproduce this short sleep phenotype in mice that exhibited decreases in NREM and REM sleep in the light phase and an increase in sleep fragmentation (He et al. 2009). Furthermore, the DEC2 mutation led to a decrease in NREM sleep following sleep deprivation and a reduction in EEG delta power confirming the involvement of this clock component in homeostatic sleep regulation. By contrast, only minimal changes in sleep were observed in *Dec2* knockout mice, although the compensatory rebound of NREM sleep after sleep deprivation exhibited considerably slower kinetics, suggesting a role for *Dec2* in the fine-tuning of sleep regulation (He et al. 2009).

3.2 Clock Gene Expression After Sleep Deprivation

During sleep, a number of genes are upregulated in the brain, and microarray analysis demonstrates that ~10 % of the transcripts in the cerebral cortex alter their expression between day and night (Cirelli et al. 2004). Many of the 1,500 genes that change expression across the 24-h day are linked to changes in behavioural state rather than to time of day differences. Surprisingly, after sleep deprivation, very few genes alter their expression; these are typically genes involved in neuronal protection and recovery (Maret et al. 2007). Sleep deprivation can also modify the expression of clock genes in areas outside the SCN. *Per* levels are elevated when sleep drive is high, which occurs independently of circadian phase (Abe et al. 2002; Mrosovsky et al. 2001). In the forebrain, both *Per1* and *Per2* mRNA levels increase after sleep deprivation in mice (Wisor et al. 2008) with a decrease in the clock-controlled gene *Dbp* (Franken et al. 2007). Clock gene expression has also been characterised in inbred strains of mice, which present differences in sleep rebound after enforced wakefulness. These studies have identified a relationship between the expression of *Per1* and *Per2* with the length of time spent awake and are consistent with a role for these clock genes in homeostatic sleep regulation (Franken et al. 2007). At the level of the EEG, changes in clock gene expression after sleep deprivation were also found to be proportional to the increase in EEG delta power across different strains of mice (Wisor et al. 2008). A potential mechanism by which sleep deprivation could alter clock gene expression has recently been described. DNA binding of CLOCK and BMAL1 to target clock genes varies over the circadian cycle in the cerebral cortex, peaking around ZT 6. Sleep deprivation was shown to reduce CLOCK and BMAL1 activation of *Dbp* and *Per2*, but not *Per1* and *Cry1*. As such, sleep history may directly regulate the circadian clock in tissues outside the SCN (Mongrain et al. 2011).

3.3 Clock-Related Genes

In addition to the core clock machinery, there are a number of clock-controlled genes which have been shown to be involved in the regulation of sleep. Expression of prokineticin 2 (*Prok2*), a putative clock-controlled output signal, is thought to be important in the transmission of circadian rhythms. *Prok2*$^{-/-}$ mice exhibit a reduction in the circadian amplitude of activity, core body temperature and sleep/wake cycle (Li et al. 2006). *Prok2*$^{-/-}$ mice sleep ~1 h 30 min less than wild-type mice over a 24-h period, changes that remained apparent under constant darkness indicating that they were not due to a masking effect of light. Remarkably, deficiency of the *Prok2*$^{-/-}$ gene modifies NREM and REM sleep in opposing directions. A reduction in NREM sleep was observed during the light period, whilst increased REM sleep occurred during both light and dark phases despite an overall reduction in total sleep (Hu et al. 2007). In these mice, NREM and REM sleep latencies were also shorter in *Prok2*$^{-/-}$ mice, indicating higher sleep pressure (Hu et al. 2007). EEG SWA during NREM sleep was comparable in *Prok2*$^{-/-}$ and wild-type mice; however, EEG theta power in REM sleep was decreased in *Prok2*$^{-/-}$ mice which also exhibited attenuated compensatory responses to sleep deprivation. These studies highlight a role for *Prok2* in the regulation of the circadian process but also in sleep homeostasis, further indicating the large degree of crosstalk between these two major processes governing the regulation of sleep.

The PAR leucine zipper transcription factor *Dbp* is under transcriptional control of CLOCK (Ripperger et al. 2000). *Dbp*$^{-/-}$ mice display a mild circadian phenotype remaining rhythmic but exhibiting a shorter circadian period (approximately 30 min) and a reduction in activity levels (Lopez-Molina et al. 1997). Total sleep duration was not altered in *Dbp*$^{-/-}$ mice, but the circadian amplitudes of sleep time and sleep consolidation were reduced, suggesting that *Dbp* may be important in altering the magnitude of the output signal from the circadian clock. REM sleep was reduced during the light period, and an increase in EEG theta frequency occurred during exploratory behaviour and in REM sleep. A normal homeostatic response to sleep deprivation was present in the absence of *Dbp*, but the accumulation of EEG delta power in the active period was reduced (Franken et al. 2000). This decrease in EEG delta power could be attributed to the slight increase in NREM sleep throughout the dark period, indicating little direct effects of *Dbp* on homeostatic sleep regulation.

Vasoactive intestinal polypeptide (VIP) signalling through the activation of the VPAC2 receptor is thought to be critical in sustaining circadian rhythms in individual SCN cells but also in the synchronisation of electrical activity between these cells (Brown et al. 2007). Mice deficient in the VPAC2 receptor gene (*Vipr2*$^{-/-}$) exhibited robust activity rhythms but showed an altered diurnal sleep/wake rhythm. Additionally, more sleep/wake transitions were evident in *Vipr2*$^{-/-}$ mice whilst total NREM sleep time was increased (~50 min) without any reported differences in NREM EEG delta power compared to wild-type mice (Sheward et al. 2010).

3.4 A Complex Role for Clock Genes in Sleep Regulation

Clock genes play a fundamental role in circadian rhythm generation, and disruption of the core clock mechanism would be expected to alter the timing of sleep; however, more surprising are its effects on the homeostatic process. Studies in transgenic mice have demonstrated that many of these genes also exert a range of effects on homeostatic sleep/wake parameters. These genetic findings are consistent with the earlier SCN lesion studies and strongly suggest that, rather than a clear separation between circadian and homeostatic processes, there is a strong interaction between these mechanisms. It will be interesting to determine how the circadian regulation of sleep is in turn affected in transgenics in which only homeostatic sleep is disturbed. In addition to their role in the core clock mechanism, it is also possible that targeted disruption of clock genes results in effects on sleep via non-circadian mechanisms. One explanation is that clock genes expressed in the SCN, responsible for the generation of circadian rhythms, are also found in other areas of the brain and cortex where they are important for regulating sleep propensity. The complexity of the findings described above, in which disruption of different clock components produces a wide range of effects on sleep, suggests that different clock genes may be involved in other molecular processes in addition to those involved in the transcriptional–translational feedback loop that generate intracellular circadian oscillations. These pleiotropic functions may directly relate to sleep or may be associated with unrelated processes such as metabolism, neurotransmission or immune functions which result in sleep disturbances (Rosenwasser 2010).

4 Regulation of Sleep by Light

The light/dark cycle provides the primary entrainment cue (zeitgeber) for the circadian system, and as a result, light will obviously modulate sleep/wake timing via photoentrainment. However, in addition to this role, acute light exposure has been shown to be involved in the regulation of sleep (Benca et al. 1998; Borbely 1978). Because of the importance of the light environment in the regulation of sleep, several groups have addressed the contribution of specific retinal photoreceptor classes in this process.

4.1 The Role of Melanopsin in Sleep Regulation

The mammalian eye serves a dual function, regulating both image-forming (IF) vision and numerous nonimage-forming (NIF) responses to light, including sleep (Lupi et al. 2008). These NIF responses to light are dependent upon retinal photoreceptors, which include the rods and cones as well as the recently identified photosensitive retinal ganglion cells (pRGCs) which express the photopigment

melanopsin (Hankins et al. 2008). Whilst many studies have focused upon the role of melanopsin in NIF responses to light, recent work by several groups has shown that rods and cones also contribute (Altimus et al. 2010; Lall et al. 2010). Mice lacking rods and cones (*rd/rd cl*) exhibit normal entrainment of sleep/wake timing and acute sleep induction in response to nocturnal light (Lupi et al. 2008). However, whilst entrainment of sleep/wake timing occurred in an attenuated form in mice lacking melanopsin photopigment ($Opn4^{-/-}$), acute sleep induction in response to a 1-h light pulse at ZT 16 was abolished. This was mirrored at a molecular level by abolition of *Fos* induction in the VLPO (Lupi et al. 2008). These findings suggested a critical role for the pRGCs in sleep regulation in response to light. In a subsequent study, Altimus et al. (Altimus et al. 2008) also reported that $Opn4^{-/-}$ mice showed no sleep induction in response to a 3-h light pulse (ZT 14–17). If, however, the data were examined in 30-min time bins, sleep did seem to occur in the first 30 min. This study also showed that mice lacking functional rods and cones ($Gnat1^{-/-}$;$Cnga3^{-/-}$) exhibited attenuated sleep induction in response to light. A mixed photoreceptor input to the sleep/arousal system was further demonstrated when mice were exposed to a 3-h dark pulse during the normal light phase (ZT 2–5) which induced wakefulness within 30 min in wild-type mice as well as in $Opn4^{-/-}$ animals and mice lacking functional rods and cones. Ablation of the melanopsin pRGCs using a transgenic model expressing an attenuated diphtheria toxin under control of the melanopsin locus ($Opn4^{DTA}$) resulted in abolition of sleep entrainment, acute sleep promotion and induction of wakefulness (Altimus et al. 2008), consistent with the hypothesis that melanopsin pRGCs form the primary conduits for irradiance detection (Guler et al. 2008). The third study by Tsai et al. (Tsai et al. 2009) found that a 1-h light pulse at ZT 15–16 failed to induce sleep in $Opn4^{-/-}$ mice, comparable with the previous two studies (Altimus et al. 2008; Lupi et al. 2008). These authors also found that a dark pulse at ZT 3–4 induced wakefulness, although this response was delayed in $Opn4^{-/-}$ animals. Additional studies using a repeated 1h:1h L:D cycle showed that the failure to demonstrate sleep induction in $Opn4^{-/-}$ mice was only apparent during the subjective night (ZT 15–21). A detailed analysis of the time course of sleep induction in response to light showed that $Opn4^{-/-}$ mice do in fact show some sleep induction in response to light but that these responses are much slower and attenuated during the dark phase (Tsai et al. 2009).

The persistence of sleep entrainment and acute sleep induction in an attenuated form in melanopsin knockout mice clearly shows that under different light stimuli, rods and/or cones are also important for sleep regulation. Whilst we now know that different photoreceptors and the quality of the light environment all contribute to sleep regulation, this relationship remains poorly defined.

5 Effects of Melatonin on Sleep

Melatonin is a neurohormone secreted by the pineal gland during the dark period of the day and has been linked with a diverse array of biological and physiological actions (Pandi-Perumal et al. 2006). The large amplitude rhythm of melatonin

represents a reliable marker of the phase of the circadian clock, transducing photoperiodic information and serving as a common humoral signal for circadian organisation (Cassone 1990; Korf et al. 1998). In addition to its chronobiotic effects, significant attention has centred on the sleep-promoting effects of melatonin and more specifically the mechanism and receptors involved. Exogenous melatonin promotes sleep in human subjects (Zhdanova 2005), although there has been controversy over its effectiveness highlighted by two contrasting meta-analyses (Brzezinski et al. 2005; Buscemi et al. 2006). The effects of pharmacological levels of melatonin on sleep in animal models present a similarly contradictory picture, with a range of studies identifying a sleep-promoting action (Akanmu et al. 2004; Holmes and Sugden 1982; Wang et al. 2003), whilst others report melatonin to be ineffective (Huber et al. 1998; Langebartels et al. 2001; Mirmiran and Pevet 1986; Tobler et al. 1994). Part of this controversy undoubtably reflects differences in dosage, time of administration and the arousal status of the subject which may preclude certain experimental protocols revealing these properties but also the subtle nature of the sleep-promoting action of melatonin.

Despite this disparity, the pharmaceutical industry has shown significant interest in exploiting the pharmacology of melatonin with a variety of melatonin agonists developed for the treatment of sleep disorders (Zlotos 2012). One of these melatoninergic compounds currently on the market is ramelteon, a non-subtype selective melatonin agonist. It exerts a sleep-promoting effect in rats (Fisher et al. 2008), mice (Miyamoto 2006), monkeys (Yukuhiro et al. 2004) and cats (Miyamoto et al. 2004). In rats, ramelteon was found to be marginally superior to melatonin in terms of the duration of action (Fisher et al. 2008), possibly reflecting its greater affinity for melatonin receptors and increased stability in vivo. Furthermore, a number of clinical studies have shown ramelteon to be effective in the treatment of both transient (Roth et al. 2005) and chronic insomnia (Liu and Wang 2012).

The mechanism responsible for the sleep-promoting effect of melatonin is not fully understood, despite the development of melatonin agonists for the treatment of sleep disorders. It is often assumed that melatonin exerts its effects on sleep through two high-affinity, G-protein-coupled receptors, MT_1 and MT_2, though until recently, it was not known which subtype is implicated in the sleep-promoting action. IIK7, a selective MT_2 receptor agonist with approximately 90-fold higher affinity for MT_2 than MT_1, promotes sleep in rats, suggesting the effects of melatonin on sleep are mediated through the MT_2 receptor (Fisher and Sugden 2009). A more recent study further confirmed a role for the MT_2 receptor in the sleep-promoting mechanism of melatonin (Ochoa-Sanchez et al. 2011). They administered UCM765, a novel partial MT_2 receptor ligand which was effective at promoting NREM sleep in wild-type and MT_1 receptor knockout mice but not in mice lacking the MT_2 receptor. In addition, pharmacological antagonism of MT_2 receptors prevented the sleep-promoting effects of UCM765, which was shown to activate neurons expressing MT_2 receptors in the reticular thalamic nucleus (Ochoa-Sanchez et al. 2011). The analysis of the sleep in MT_1 and MT_2 deficient mice in this study revealed a complex phenotype that certainly warrants further investigation, particularly since removal of endogenous melatonin in rats has little or no effect on total sleep time or sleep/wake cycle regulation (Fisher and Sugden 2010; Mendelson and Bergmann 2001).

6 Regulation of Sleep by Social Cues

Unlike the homeostatic, circadian and photic mechanisms, the role of social cues in the regulation of sleep is more poorly understood. Due to the methods used to study sleep, animals are typically singly housed. However, a number of studies have addressed the impact of social cues on the regulation of sleep, and from this work, it appears that social interaction plays an often overlooked role in the regulation of sleep. Studies on social stimuli have been used to evaluate the effects of the quality of wakefulness on subsequent sleep (Meerlo and Turek 2001). Social conflict, where male mice were placed with an aggressive dominant male for 1 h in the middle of the light phase, produced dramatic effects on subsequent NREM sleep. EEG SWA, indicative of NREM sleep intensity, was significantly increased for 6 h and the effects on NREM sleep duration lasted for 12 h. REM sleep was suppressed during the subsequent light phase after the encounter, followed by a recovery-phase rebound. By contrast, sexual interaction, where male mice were placed with an oestrous female, produced only mild suppression of both NREM and REM sleep following the interaction. Blood sampling in this study suggested that an elevation in corticosterone may account for the temporary suppression of REM sleep (Meerlo and Turek 2001). Further studies in rats have shown that a similar social defeat model produces increases in EEG SWA, suggesting that this acute stress may increase the rate of sleep debt accumulation (Meerlo et al. 1997). To test this hypothesis, subsequent sleep deprivation was employed. Animals underwent either 1-h social defeat with 5-h sleep deprivation or 6 h sleep deprivation with no social defeat. EEG SWA was found to be higher following social defeat, illustrating that in addition to the duration of wakefulness, what is experienced during waking also modulates sleep intensity (Meerlo et al. 2001). A recent study assessed the impact of social context on sleep deprivation and EEG SWA in C57BL/6J mice (Kaushal et al. 2012). They found that that socially isolated mice exhibited a blunted homeostatic response to sleep deprivation compared to paired mice which was associated with higher anxiety levels.

Studies on environmental enrichment have suggested that rats housed in highly enriched cages exhibit longer bouts of sleep (Abou-Ismail et al. 2010), although EEG validated behaviour was not assessed in this study. An earlier study (Mirmiran et al. 1982) showed that juvenile rats raised in enriched conditions showed increased sleep time and shorter sleep latency when compared with animals housed under standard or isolated rearing conditions. Whilst limited, these studies suggest that the nature of the waking experience has a large impact on the modulation of subsequent sleep.

Earlier work by Michaud et al. (1982) found that the total amount of NREM and REM sleep was decreased when rats were placed into a novel individual cage. Other studies in mice have examined the effect of two types of environmental novelty on activity and sleep in mice. A cage change or the introduction of novel objects increased activity and NREM sleep onset latency and decreased both NREM and REM sleep time (Tang et al. 2005). The effects were relatively long-lasting with reductions in NREM sleep reported for up to 3 h after changing cages (Tang et al. 2005).

Changes in the sleeping environment can also produce significant alterations in human sleep behaviour. This is classically termed the 'first-night effect' which can be observed in individuals on the initial night of exposure to the unfamiliar surroundings of a sleep laboratory (Le Bon et al. 2001). This response to a novel environment results in an increase in arousal and vigilance characterised by an increase in NREM and REM sleep latencies together with a moderate reduction in REM sleep and a decrease in overall sleep efficiency (Shamir et al. 2000).

7 Practical Applications

The sleep/wake cycle is a complex physiological process, controlled by both circadian and homeostatic mechanisms. In addition, sleep is also regulated by the light/dark cycle, melatonin and social timing. These interactions may be summarised as a conceptual model as shown in Fig. 3, in which these internal and external mechanisms interact to modulate overt sleep behaviour. Finally, we will consider the role of sleep in two specific research areas which have broader implications for research beyond the circadian field. In addition, the reader is directed to a recent review summarising the links between clock genes and sleep and their relevance to energy metabolism, neuronal plasticity and immune function (Landgraf et al. 2012).

7.1 Sleep and Mental Health

Due to the number of brain regions and neurotransmitters involved in the regulation of sleep, it is becoming increasingly apparent that abnormal sleep is a significant comorbidity in many neuropsychiatric and neurodegenerative diseases (Wulff et al. 2009, 2010). These findings have widespread implications, not least that disturbances in mood, cognition, metabolism and social interaction may be further exacerbated by disturbances in sleep. In addition, the abnormal neurotransmitter release, stress-axis activation and medication may further destabilise the sleep/wake cycle. The complex interaction between mental health disorders and sleep is not well understood. However, it has been proposed that stabilisation of sleep in psychiatric and neurodegenerative disease may be an important means by which the devastating symptoms of these conditions may be ameliorated (Wulff et al. 2010). Clock genes have also been linked to human psychiatric disorders, and mutations have been associated with altered affective behaviour in animal models (Rosenwasser 2010). Arguably the best example of this is the *Clock*-mutant mouse, which has been proposed as a model for mania. *Clock*-mutant animals display hyperactivity, decreased sleep, lowered depression-like behaviour, lower anxiety and an increase in reward-oriented behaviour (Roybal et al. 2007). In addition,

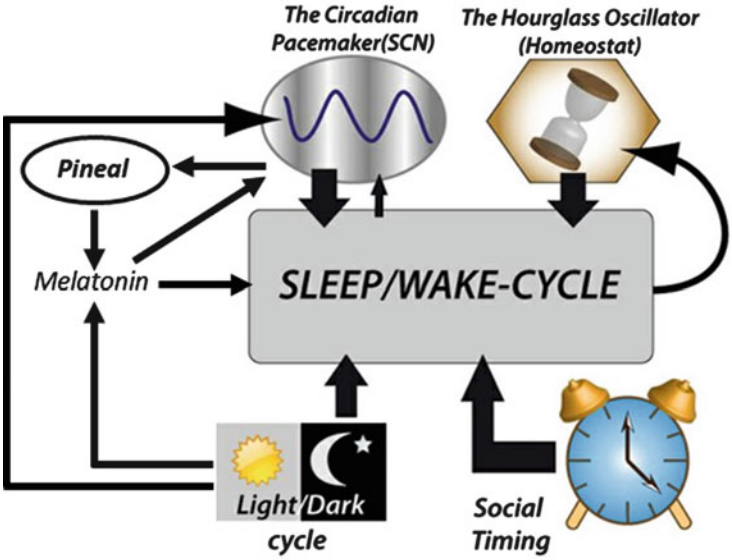

Fig. 3 Diagram illustrating the key components in the generation and maintenance of the sleep/wake cycle. Sleep is regulated by two broad mechanisms involving both the 24-h body clock (circadian system, known as process C) and a wake-dependent homeostatic build-up of sleep pressure (also called process S). The circadian pacemaker located within the suprachiasmatic nuclei (SCN) coordinates the timing of wakefulness throughout the day and sleep during the night. This 24-h rhythm interacts with the homeostatic drive for sleep, whereby the sleep pressure increases during wake and dissipates during sleep. This process has been likened to an 'hourglass oscillator'. The circadian and homeostatic drivers regulate the multiple neurotransmitter and brain systems involved in sleep and arousal. Sleep/wake behaviour in turn feeds back upon the circadian pacemaker and homeostat. These components are modulated by light which acts to entrain the circadian pacemaker to the environmental light/dark cycle, acutely suppress melatonin production from the pineal and acutely elevate or suppress levels of arousal. Finally, social activities will also modulate sleep/wake activity

disrupted circadian rhythms have recently been described in a mouse model of schizophrenia, the Bdr mutant. This mutation affects synaptosomal-associated protein (Snap)-25 exocytosis, resulting in schizophrenic endophenotypes that are modulated by prenatal factors and reversible by antipsychotic treatment (Oliver et al. 2012). These findings further suggest a mechanistic link between sleep and circadian rhythm disruption and neuropsychiatric disease (Pritchett et al. 2012). Researchers working in the mental health field should be aware that sleep disturbances are often prevalent in this patient population. Due to the common neurotransmitter systems underlying these conditions, even animal models may display disturbances in sleep and arousal which may affect the outcome of behavioural research.

7.2 Behavioural Testing

Behavioural testing in rodents is widely used in neuroscience research. One factor that is typically overlooked in many routine phenotyping assays is the state of arousal of the animals being tested. Increased arousal results in enhanced performance, up to a peak, beyond which a deterioration of performance occurs, as described by the Yerkes–Dodson Law (Yerkes and Dodson 1908). As such, animals with a low level of arousal will perform at a lower level, whereas those with a higher state of arousal will always outperform their controls. Altered states of arousal may arise from changes in homeostatic sleep drive (and previous sleep history) as well as differences in alertness due to circadian rhythm disturbances. In addition, differences in photosensitivity or responsiveness to stress (such as handling) may also give rise to altered states of arousal. As a result, behavioural testing should take into account both the sleep and circadian phenotype, including differences due to background strain (Franken et al. 1999). Furthermore, the prevailing light environment and retinal integrity as well as social and environmental modulation of arousal should all be considered (Peirson and Foster 2011). Failing to account for the state of arousal during behavioural testing can give rise to misleading results, where differences in performance are simply due to the differences in arousal state between control and experimental animals.

8 Conclusions

Whilst great advances have been made in our understanding of the circadian control of sleep via clock gene transgenics, understanding the homeostatic regulation of sleep remains an area of much ongoing research. Details of the mechanisms underlying the regulation of sleep by the light environment and social interaction also remain poorly defined. In addition to understanding the role of these various processes independently, future work will need to determine their relative contribution under natural conditions to enable us to truly understand the mechanisms influencing and giving rise to sleep and wakefulness.

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