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Genomic imprinting and the control of sleep in mammals

Glenda Lassi[1] and Valter Tucci[2]

Recent epigenetic studies suggest that genomic imprinting is crucial in the biology of sleep. Sleep is a physiological process that is governed by homeostatic and circadian mechanisms, and here we review evidence that both mechanisms are influenced by imprinted regulatory processes. A growing number of imprinted genes are being associated to direct and indirect control of sleep, and in some cases, thermoregulation represents an important metabolic component for the interplay between imprinted mechanisms and sleep physiology. Moreover, it is a new striking phenomenon that we discovered that sleep traits follow parent-of origin inheritance. Parental genome is important to the extent that it can determine whether a gene is either homeostatically regulated or not, in response to sleep loss. Therefore, it is now clear that the association between genomic imprinting and sleep exists. However, the experimental work towards the link between sleep and imprinting is just at its early stages, the next years will be pivotal to fully understand whether the genomic imprinting hypothesis of sleep can lead to major discoveries and, perhaps, to unravel the mysteries of sleep.

Addresses
[1] Clinical Development Unit, Early Clinical Development, IMED Biotech Unit, AstraZeneca, Cambridge, UK
[2] Department of Neuroscience and Brain Technologies (NBT), Genetic and Epigenetics of Behaviour – Istituto Italiano di Tecnologia, via Morego 30, 16163 Genova, Italy

Corresponding author: Tucci, Valter (valter.tucci@iit.it)

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Introduction

To date, there have been about 200 imprinted genes identified in mammals. Imprinted genes (i.e. differentially expressed genes depending upon parental origin) have major effects on prenatal and postnatal development and play a role in survival and growth. These genes have been implicated in a number of physiological and behavioural vital functions such as maternal care, metabolism, and thermogenesis [1].

In this review, we will focus on the emerging field of genomic imprinting and sleep. We will discuss evidence showing the impact of imprinted genes on sleep due to thermoregulatory processes in mammals. The modulatory role of imprinting on sleep appears pivotal in evolution, yet only few studies have investigated it.

The research on the genetics of sleep has mainly focused on the role of single genes in behavioural and electrophysiological determinants of sleep states. Human twin studies, along with investigations in several mouse models, have shown that EEG traits (See Box 1) are heritable and therefore imputed by a genetic component. For example, power spectra at the 8–16 Hz frequency during NREM sleep, in humans [8], and delta power rebound after sleep deprivation, in mice [9], follow mendelian genetics transmission. A single gene modification can cause a sleep disorder such as, for example, the fatal familial insomnia, which is an autosomal dominant inherited prion disease of the brain [10]. Moreover, many of the so-called 'sleep genes', such as immediate early genes (e.g. *Arc*, *c-Fos*, and *Homer1a*) are differently expressed according to the vigilance state [11–20], but with little attention paid as yet to epigenetic factors that can regulate their expression.

Non-mendelian parent-of-origin expression of sleep

An unexpected observation in the study of sleep was the evidence that sleep homeostasis is regulated by the allelic combination of the genetic background in mice [21]. Sleep homeostasis is normally triggered by sleep loss, which causes rebound expression such as increase in specific electrophysiological measures (e.g. delta sleep). Several studies have also demonstrated that homeostatic responses apply to the expression of several genes and although it was reported that genetic background influences this process [22–24], all studies until recently focused on classical mendelian aspects. For example, pioneering investigations on sleep in inbred mice, in the early' 90s, reported that AKR/J mice show a high rebound after 6 hours of sleep deprivation, while DBA/2J mice show only a mild response [22]. In our lab we studied the reciprocal crosses of the AKR/J and DBA/2J lines, and we found differences in gene expression rebound [21] and have now confirmed these results matched by electrophysiological signatures (unpublished data, not shown). In particular, we observed that specific high band frequencies, which are associated to REM sleep, respond differently between different hybrid cohorts. In our previous work we found nine genes that were differentially regulated in AKR/JxDBA/2J sleep-deprived F1 mice and 7 genes differentially regulated in DBA/2JxAKR/J sleep

Box 1 Sleep

Sleep occurs with a daily periodicity (i.e. circadian) that is coupled with the physiological homeostatic control of several parameters. It is characterized by temporary absence of movements, reduced sensitivity to stimuli and metabolic changes; several genes change their expression profile during sleep and recently identified epigenetic processes, for example DNA methylation, seem to play an important role in setting both circadian and sleep homeostatic processes [2,3,4••]. From a neuroscience perspective, sleep is thought to influence single neuronal and network activity, therefore contributing to brain processes such as those involved in memory and more general cognitive aspects [5,6].

Sleep architecture is traditionally constituted by two main vigilance states studied, so far, in many mammals: non-rapid eye movements (NREM) and rapid eye movements (REM), which are distinguished by electrophysiological, behavioural and metabolic differences (Figure 1). In wakefulness the electroencephalogram (EEG) activity is typically desynchronized as it captures the intense brain activity involved in several behavioural events during the subjective day, while the electromyogram (EMG) reflects the motor activity in response to behaviours. As we progress into sleep from wakefulness, the EEG gradually becomes more synchronized and is dominated by slow-waves, namely *delta* waves, 0.5–4 Hz, that are typical of NREM sleep. NREM sleep is characterized by an EEG signal with low frequency and high amplitude and a reduced EMG tone. The delta range of EEG frequencies is a marker for sleep pressure, that is, the need to sleep. The computation of its power, which is obtained by calculating the Fast Fourier Transform (FFT), is a reliable index of sleep pressure and mirrors sleep homeostasis. The delta power linearly increases as wakefulness progresses and it decreases with the fulfilling of sleep. In contrast, REM sleep, which occurs subsequent to NREM sleep, is characterized by an active EEG, similar to wakefulness and an atonic EMG. Electrophysiologically, REM sleep is characterized by theta waves (5–7 Hz) and the EMG exhibits both atonia in postural muscles and phasic events such as the rapid eye movements and limb twitches. During REM sleep, mammals reduce the control of body temperature and increase their energy expenditure, a phenomenon that so far has been in contrast with the idea that sleep could serve as period for energy conservation [7].

deprived F1r mice [21]. Bioinformatical predictions of specific upstream mechanisms for the regulation referred to signalling pathways (i.e. DICER1, PKA) growth factors such as CSF3 and BDNF, and transcriptional regulators, for example EGR2 and ELK4, that were modulated by parental effects.

Although many biological phenomena can cause parent-of-origin effects, the most well-known epigenetic non-mendelian phenomenon is genomic imprinting.

Imprinted genes and sleep

The first evidence of a modulation of an imprinted gene in sleep was reported in mice. In 2012 we published a study that showed that the imprinted gene *Gnas* is involved in the physiological, metabolic and cognitive processes underlying NREM and REM sleep [25]. In particular, mice carrying the loss of imprinted expression of *Gnas* that resulted in the biallelic expression of *Gnas*, exhibited dramatic changes in sleep and sleep-mediated traits. *Gnas* encodes the stimulatory G-protein subunit Gs, which is involved in the generation of intracellular cyclic AMP and plays a crucial role in both central synaptic transmission in the brain and energy expenditure, as well as in metabolism by mediating peripheral sympathetic effects. G protein-coupled receptors (GPCRs) represent the largest family of membrane proteins expressed in the brain, approximately 800 genes codes for GPCRs and exert fundamental roles in neuronal communication (acting both in pre-synaptic and postsynaptic terminals) [26]. Among the variety of GPCRs that are known, there is also a whole range of adenosine receptors (ARs) that mediate the effects of adenosine through neurotransmission [27]. Interestingly, *Gs* couples specifically with A_{2A}Rs, which are highly expressed in striatum but are also expressed in cortex and hippocampus. A_{2A}Rs are pivotal in hippocampal neuronal transmission and facilitate long term potentiation (LTP) and memory formation [28,29]. A number of lines of evidence in sleep biology indicates that adenosine is an endogenous factor that promotes sleep [30,31]. Importantly, the main effects of adenosine in sleep and, in particular, in NREM regulation are selectively mediated by A_{2A}Rs by means of prostaglandin distribution in the brain [32,33].

Gnas is maternally expressed and paternally repressed in a subset of tissues and brain areas. Imprinted expression of *Gnas* is controlled by a cis-acting differentially methylated region (DMR): the Exon1A-DMR. Paternal transmission of a deletion of the Exon1A-DMR (Gnastm1Jop, hereafter called Ex1a) causes derepression of the normally repressed paternal *Gnas* allele in imprinted tissues resulting in biallelic *Gnas* expression and loss of imprinting.

The +/*Ex1a* deleted mice exhibited an increased delta power in NREM sleep at baseline compared to littermate controls, but not subsequent to sleep deprivation. Furthermore, the most striking effect on sleep was observed in the expression of REM sleep, perhaps due to a thermoregulatory effect. REM was remarkably reduced in +/Ex1a mice compared to controls. After sleep deprivation, the major rebound in mutant mice was observed in REM sleep, which confirms the need for a homeostatic recovery of REM. In addition, during baseline conditions when animals lived undisturbed, mutant mice showed higher accuracy and time precision in a behavioural task that assesses high cognitive performance. This result is in agreement with the increased delta sleep in this phase. Indeed, the beneficial effect of delta sleep in cognitive performance is widely reported in literature [6]. On the contrary, mutants showed a deficit in response to fear, which is a primitive and hippocampus-mediated behaviour. The induction of fear caused an increase of REM sleep, the following night, only in wild-type mice as expected but not in mutants. Within the framework of literature regarding the memory consolidation in sleep [34], this result can be interpreted as a lack of sleep-