Review

Sleep and its disorders in translational medicine

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Abstract

The study of sleep is a useful approach to studying the brain in psychiatric disorders and in investigating the effects of psychotropic drugs. Sleep physiology lends itself well to pharmacological and physiological manipulation, as it has the advantage of a functional output, the electroencephalograph, which is common to all mammals, and can be measured in freely moving (or naturally sleeping) animals under controlled laboratory conditions or in a naturalistic home environment. The complexity of sleep architecture varies between species but all share features which are comparable. In addition, sleep architecture is sensitive to changes in brain neurotransmitters such as serotonin, so cross-species sleep measurement can be combined with pharmacological manipulation to investigate the receptor mechanisms controlling sleep–wake regulation and sleep architecture in response to known and novel agents. Translational approaches such as these have improved our understanding of sleep circuitry and facilitated the development of new treatments for sleep disorders, particularly insomnia. This review provides examples of how research findings within the sleep field have been translated between animal models, healthy volunteers and patient populations with particular focus on the serotonergic system.

Keywords

Antidepressants, drug development, insomnia, sleep, translational, serotonin

Introduction

Sleep is a complex physiological process within the brain which it is highly regulated and controlled. It is becoming apparent that good sleep is essential for normal brain function and for our overall health and well-being. Sleep was considered to be entirely a passive experience, to provide rest to the brain and body, until studies in the 1950 s revealed the existence of rapid-eye movement (REM) sleep; electroencephalography (EEG) studies of the human brain revealed paradoxical high EEG activity resembling wake during REM sleep (Aserinsky and Kleitman, 1953). Since then, the true nature and function(s) of sleep has been the subject of intense study.

Research over the past 25 years has discovered that the human sleep–wake cycle is controlled by a series of complex but interacting brain mechanisms that serve to control the timing of sleep, its structure, depth and duration. Two separate but interacting processes were identified that control sleep timing (Borbely, 1982); the circadian process (C process) and the homeostatic, or sleep-dependent recovery process (S process). The circadian process is that which regulates the daily rhythms of the body and brain. The main circadian pacemaker is found within the suprachiasmatic nucleus (SCN) of the hypothalamus (for review see Golombek and Rosenstein, 2010). The SCN displays an oscillatory pattern of activity that is driven by a transcriptional–translational feedback loop (Jin et al., 1999), such that its activity is innate and self-sustaining; the cells continue to demonstrate cyclical activity even in isolation from the rest of the body. The oscillatory pattern of activity has a period of approximately 24 hours, and this drive from the SCN also co-ordinates the activity of peripheral clocks of other organs to control all biological rhythms within the body. The SCN is strongly influenced by light entering the eye and, to a lesser extent, by other time cues such as temperature. Bright light in the evening will delay the clock and bright light in the morning is necessary to synchronize the clock to a 24-h rhythm; constant light or darkness lengthens the cycle to about 24.3 h in humans. The circadian process functions to ensure that sleep occurs at a time that is ecologically favourable.

By contrast, the homeostatic process is wake dependent; it increases in depth and duration in relation to the amount of time since last sleep, and it dissipates with subsequent sleep. The homeostatic process is controlled by a centralized interaction between wake and sleep-promoting centres of the

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hypothalamus and brain stem (Saper et al., 2005) and may also be controlled by localized mechanisms whereby brain regions can obtain differential recovery sleep, dependent on prior levels of activity (Huber et al., 2004).

These two processes interact to promote the onset of sleep when both are high (at the usual bedtime), and maintain sleep when the circadian process is high and the homeostatic process is declining (in the small hours). The integration of the homeostatic and circadian processes to control the sleep–wake cycle is performed by a network of brain nuclei that interact in a complex fashion (Dijk and von Schantz, 2005; Saper et al., 2005). These networks are influenced by pharmacological manipulation and are studied in great depth to facilitate the development of novel pharmaceuticals for sleep–wake disorders. It is thought that being aroused, anxious or alert may overcome the homeostatic and circadian processes, and may be one of the main mechanisms involved in the complaint of insomnia. Elements of the circadian and homeostatic mechanisms may also become involved, particularly where the insomnia is of long standing and is complicated by behaviours which weaken these processes, such as irregular bedtimes.

Much of the research mentioned above has only been made possible because of the ability of sleep researchers to measure and manipulate the sleep–wake cycle in animals. Shared features of the sleep EEG and of brain circuitry between animals and humans, particularly rodents, have facilitated this research. Good examples include the elegant demonstrations of shifting circadian cycles after phase-delay, phase-advance or by melatonin agonists (Wisor et al., 2009; Yannielli and Harrington, 2004), and the intriguing finding that just a short burst of bright light within otherwise complete darkness is sufficient to entrain the circadian clock to a 24-h rhythm (Rea et al., 2008). The many novel hypotheses generated from such experiments regarding the control of circadian rhythms, the sleep–wake cycle and the pharmacology of known and novel sleep-promoting compounds, can best be tested in humans if the findings can be directly translated between suitable experimental paradigms. This is where the development of translational models becomes important.

Modelling human sleep in animals

The efficacy of novel drugs for sleep disorders must be determined during the preclinical phase of drug development in order to screen the best candidates and predict effects in humans. Whilst individual components of sleep–wake physiology can be reproduced in vitro, such as SCN oscillation in a petri dish (Liu and Reppert, 2000), sleep is a complex physiological state that requires in vivo models.

The complexity of sleep in humans would seem distant from the rest–activity patterns of simple organisms. However, even simple creatures share features of a sleep–wake or rest–activity cycle. All animals have an innate circadian clock generated by a group of cells with homology to the SCN, and their period and timing are dependent on particular gene expression, most of which are common to fruit flies, mice, primates and many other species. Polymorphisms of these genes that lead to an altered circadian rhythmicity or sleep homeostasis are particularly easy to identify in fruit flies, and similar variants of these genes have subsequently been found to alter sleep in healthy people, for example the *per3* gene (Viola et al., 2007), and those with certain disorders of circadian rhythm, for example *per 2*, *per3* and *S662G* clock genes (Ebisawa, 2007).

Indeed, much of the information which we now have about the human genes controlling circadian function comes from experiments with fruit flies (for review see Cirelli, 2009). These experiments were then developed to study homeostatic mechanisms, using mechanical stimulation to produce rest deprivation and recovery rest. Even in these simple organisms, the differential contribution of the circadian and homeostatic mechanisms to the rest–activity cycle can be demonstrated. Drug effects have also been studied. For example, the effect of the wake-promoting drug modafinil has been found to have similar effects to that found in humans (Hendricks et al., 2003). The benefits of using fruit flies as a model for sleep lie in the ease of conducting genetic manipulation, cost and time efficiency and with reduced ethical implications as compared with using rodents or other higher species. However, the lack of a REM sleep component and the profound differences in neuroanatomy and neurochemistry seriously limit the application of this model to the human condition.

Rodent models provide a significantly better option for studying the neuroanatomical and neurochemical components of the sleep–wake cycle and for determining the brain circuitry involved in normal sleep and disease states. Mouse models provide the opportunity to develop knock-in and knockout genetic manipulations to investigate the relationship between a particular receptor system and sleep phenotype, and rat models have a greater utility for those studies requiring pharmacological manipulation or EEG and electromyography (EMG) measurement due to their increased brain size and cognitive capacity. Examples include the pharmacological characterization of 5-HT_{2A} receptor involvement in the sleep–wake cycle (Popa et al., 2005), and subsequent testing of related treatments for insomnia in rats and healthy volunteers (Al-Shamma et al., 2010), the use of a rat model to extend the finding of learning-dependent increases in sleep spindle density during non-REM sleep in humans (Eschenko et al., 2006; Gais et al., 2002), the demonstration of GABA-A receptor subunit-specific actions of gaboxadol to elicit changes in sleep EEG spectra (Winsky-Sommerer et al., 2007), and the use of pharmacological manipulation to investigate the brain pathways involved in sleep and anaesthesia (Lu et al., 2008; Nelson et al., 2002). Even so, such models pose several challenges for translational research. There are marked differences between rodent and human sleep patterns. Humans have monophasic sleep, that is, sleep is usually taken in one session during a 24-h period, but the sleep of mice and rats sleep is polyphasic. The various different phases of non-REM sleep seen in humans are not easily distinguishable in mice and rats, and the sleep cycles incorporating orderly progression of these stages are shorter and more fragmented. In addition, there are the usual problems of dose translation that complicate the comparison of pharmacological effects between species.

Despite these differences, sleep parameters that we commonly measure in human subjects such as sleep onset latency

(SOL) REM onset latency (ROL), slow-wave activity, total sleep time and number of awakenings can easily be measured in rats, and the effect of pharmacological challenges on these parameters in rat is a good predictor of likely human response. This is where the effective use of translational medicine can be best utilized. Indeed, the rapid screening of novel pharmaceuticals for their efficacy in promoting sleep or wake in rodents has become an important step in determining which drugs are taken forward into human studies for the treatment of sleep–wake disorders, particularly insomnia where there are now a number of potential treatments in the pipeline (Wafford and Ebert, 2008).

The logical extension of such studies is to use rodent models of sleep disorders to investigate novel drug mechanisms and accelerate drug discovery further. Until recently, rodent models had not been widely used to model sleep disorders, but there are now several examples reported in the literature, including those for primary insomnia (Revel et al., 2009; Seugnet et al., 2009), obstructive sleep apnoea (Veasey, 2009), restless legs syndrome (Qu et al., 2007), narcolepsy (Chen et al., 2009) and in disease-related sleep disturbance such as Huntington's disease (Bode et al., 2009), Parkinson's disease (Garcia-Garcia et al., 2005; McDowell et al., 2010) and Alzheimer's disease (Wisor et al., 2005).

The problem of insomnia

Insomnia is a significant, growing problem for which few effective treatments exist. It is a multi-factorial condition which is difficult to simulate in animal models for several reasons; the diagnosis of insomnia in humans is made on clinical grounds based purely on the subjective complaint of the patient that their sleep is unsatisfactory and leads to daytime dysfunction, and also, in primary insomnia, the cause of the complaint is not usually tangible or measureable. Studies of the prevalence of insomnia in the general population demonstrate a median prevalence for all insomnia of about 35%, with a range of 10–15% being assessed as moderate to severe disorders (Sateia et al., 2000). In many cases, treatment is required. The non-benzodiazepine 'Z' drugs (zolpidem, zaleplon and zopiclone) are efficacious in the treatment of insomnia, particularly in the short term (Buscemi et al., 2007). Insomnia is a long-term disorder; in a large UK survey 69% of those with insomnia still reported insomnia 1 year later (Morphy et al., 2007), and chronic conditions require longer-term treatment for which the benzodiazepines and sedative antidepressants are often prescribed. The side effects of these drugs mean that there is still huge potential for the development of hypnotics that do not produce detrimental daytime consequences (such as sedation, drowsiness) or dependence.

Recent advances in the understanding of sleep and the subsequent emergence of novel drug targets ensure the future identification and development of improved sleep therapies (US Department of Health and Human Services National Sleep Disorders, 2003; Wafford and Ebert, 2008). For translational medicine, we are particularly concerned with optimizing the use of available models to reflect the human condition and thus accelerating basic research findings into the clinic. Inducing artificial sleep disturbance to produce a predictive model of insomnia in which to test efficacy of novel drugs may therefore be preferable to using normally sleeping volunteers or animals, in order to maximize the chance of observing a response to treatment. Insomnia symptoms have been modelled using several methods in rats, such as suspending the home cage above water, the first-night effect, chronic mild stress (predator smell, etc), phase shifting or continuous/intermittent noise-induced sleep disruption (for review see Revel et al., 2009). These models display varying degrees of success in terms of their ability to reliably produce insomnia-like symptoms, and in their response to proven insomnia drug treatments.

There is a further need for models to be applicable to human studies that will allow for direct comparisons between species, so that compounds can be assessed earlier in drug development and outcome in humans predicted. Using an efficacy model to predict outcome in healthy volunteers, rather than insomniacs, could minimize confounders that affect sleep such as age, weight and gender and also reduce the difficulties associated with recruitment and variability encountered in patient trials. Some of the models described above are easily transferable to healthy volunteers, for example using phase-advance or first-night effect to mimic sleep onset insomnia, or noise to induce sleep-maintenance insomnia. These have been successfully used in early studies in volunteer models evaluating GABA-A receptor agonists such as benzodiazepines, zopiclone, zolpidem and zaleplon (Cluydts et al., 1995; Erman et al., 2001; Stone et al., 2002; Walsh et al., 1990). One study has used a post-nap model of insomnia in healthy volunteers to evaluate the efficacy of a novel 5-HT_{2A} inverse agonist and compared results directly with that found in rats (Al-Shamma et al., 2010).

Studies with caffeine as a sleep-disrupting agent have proved useful in developing a model of insomnia which is successfully translated from animal to healthy volunteer to insomnia patients. The model was validated by two effective sleep-promoting agents, with different pharmacology, zolpidem and trazodone. Zolpidem is a hypnotic and allosteric modulator of the GABA-A receptor, acting selectively at the α1 subunit to increase GABA function. Trazodone is an antidepressant with sleep-promoting actions. These effects are probably due to its property of blocking 5-HT_2 receptors, since other 5-HT_2 antagonists also improve sleep (Hicks et al., 2002; Landolt et al., 1999; Sharpley et al., 1990), particularly 5-HT_{2A} selective ligands (Monti, 2010). At higher doses trazodone also acts as an antagonist at α1 and α2 adrenergic receptors and H1 histaminergic receptors, which could contribute to its sleep-promoting effects (Cusack et al., 1994), but other selective drugs within these pharmacological categories have different sleep profiles to trazodone; they either do not promote slow-wave sleep or have REM effects (Wilson and Argyropoulos, 2005). In rats, radiotelemetry transmitters with electroencephalogram and electromyogram electrodes were implanted for sleep recording. Animals were orally administered caffeine alone (10 mg/kg) or in combination with zolpidem (10 mg/kg) or trazodone (20 mg/kg), or vehicle, in crossover experiments. Home polysomnography was performed in 12 healthy male volunteers in a randomized, placebo-controlled, 4-week crossover study. Subjects received placebo, caffeine (150 mg) or caffeine in combination with

zolpidem (10 mg) or trazodone (100 mg). Subjective sleep effects in volunteers were assessed using the Leeds Sleep Evaluation Questionnaire. Caffeine caused a significant disruption of objective sleep in rats and humans (Paterson et al., 2007, 2009a, 2009b). This effect was sensitive to zolpidem and trazodone, both of which attenuated the caffeine-induced disruption. Furthermore, both hypnotics restored the worsening of subjective measures of sleep onset caused by caffeine in volunteers. A very similar experiment, but without caffeine, was then performed in 12 patients with DSM-IV chronic insomnia, comparing the same dose of trazodone with placebo (Paterson et al., 2009c). Significant sleep-improving effects were seen, similar to those in caffeine-treated volunteers (Figure 1).

The model does not address the problems of sleep maintenance, however; no significant change in sleep continuity parameters were seen after caffeine in healthy volunteers, changes which were evident in the insomniac patient population. In addition, sleep was assessed in response to short-term (single dose) treatment only, which does not address the possibility of tolerance effects, or of longer-term changes in sleep architecture which may impact on efficacy with chronic treatment. In the case of the caffeine experiments, similar effects were seen in rats, in healthy subjects and in patients, which appears to represent a good example of translation. It should be noted that the doses of drugs administered in animal models are often not directly applicable to the efficacious human dose, which can cause problems with data interpretation, especially where the study drug may have multiple binding sites at higher doses, as is the case with trazodone. Data interpretation must therefore be undertaken with care (see discussion within Paterson et al., 2009a, 2009b).

Studies with other sleep-inducing agents have not translated so well. Clonidine is an example, for in rats the α_2-adrenoceptor agonist is a remarkably effective sleep-inducing agent (Drew et al., 1979), but in man, although it reduces alertness, it does not precipitate sleep and subjects are easily alerted (Hou et al., 2005). Interestingly though, it has been reported to ameliorate a disorder of REM sleep, REM behaviour disorder (Nash et al., 2003).

In the last 8 years the discovery of the crucial role played by orexins and their receptors in the control of wakefulness and sleep in both animals and humans has proved to be one of the leading examples of translational sleep research. The simultaneous publication of findings of abnormal orexin receptors in dogs with familial narcolepsy (Lin et al., 1999), and of cataplexy-like symptoms in orexin knockout mice (Chemelli et al., 1999), was followed the next year by the revelation that patients with narcolepsy had absent orexin in cerebrospinal fluid (Nishino et al., 2000). This work led to an explosion of research in the field of narcolepsy and also in other sleep disorders. Orexin is secreted during waking in animals, and there are orexin receptors in the hypothalamus. The hypothalamus is important in maintaining stable wakefulness (Saper et al., 2005). Therefore orexin receptors are also considered to be a target in the treatment of insomnia, where excessive wakefulness is a problem. The first report of an orally available orexin receptor antagonist (ACT-078573) describes its effects on sleep in the first-into-man study, as well as in rats and dogs (Brisbare-Roch et al., 2007). The authors measured objective sleepiness in the day and found that both humans and animals studied in the normally active period fell asleep more readily and were generally sleepier after dosing with ACT-078573. These studies show

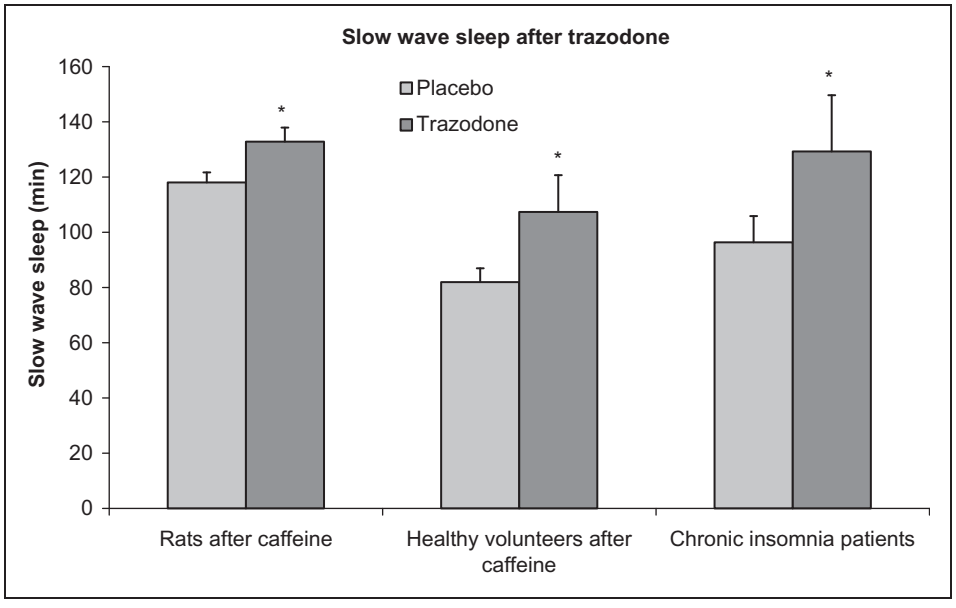

Figure 1. Effect of trazodone on slow wave sleep in rat, healthy volunteers with caffeine-induced insomnia and patients with primary insomnia. Data are amount of slow wave sleep (minutes of stage 3 and stage 4 ± S.E.M) during the whole sleep period for healthy volunteers and patients, and non-REM sleep (min) during the first 6 h of recording in rats. *Values are significantly different from placebo ($p < 0.05$, Student's paired *t*-test). Doses of trazodone are 20 mg/kg (rat) and 100 mg (healthy volunteers and patients). Data are taken from Paterson et al., 2009a, 2009b and 2009c.

that using sleep as a marker in preclinical studies of new compounds for insomnia is promising. Following a successful dose-ranging study (Hoever et al., 2010), phase III clinical trials of almorexant are now underway.

Other sleep disorders

In less common disorders of sleep where the potential market is smaller, there is nevertheless much interest in developing new drug treatments. A major cause of hypersomnia, or excessive daytime sleepiness, presenting at sleep clinics is caused by changes in the upper airway during sleep (obstructive sleep apnoea (OSA)). Narrowing of the airway during sleep leads to hypoxia, which then triggers an awakening, and these frequent and numerous awakenings deprives the patient of sleep and makes them sleepy during the day. OSA is usually treated with physical means such as continuous positive airway pressure (CPAP). The narrowing of the airway has two elements, one anatomical and the other physiological, so that people with a narrower airway than normal also have an abnormal reflex dilatory response to the further narrowing that occurs during sleep, especially REM sleep. Studies of this reflex response in rodents led to findings that neural control involves serotonergic mechanisms (Besnard et al., 2007); withdrawal of 5-HT excitatory drive during sleep may therefore reduce upper airway size. Administration of serotonergic agents to increase 5-HT tone during sleep has been tried in humans but with only modest or negative results; for example, a single report of beneficial use of the serotonergic agent mirtazapine in a patient with OSA who refused CPAP (Castillo et al., 2004) was followed by a small randomized trial which reported halving of nighttime apnoeas and hypopnea in patients with OSA (Carley et al., 2007). Unfortunately, two more randomized trials did not replicate these results or change daytime sleepiness (Marshall et al., 2008), and since mirtazapine causes daytime sedation and weight gain it was not recommended in these patients. Other drugs acting on serotonin, such as the selective serotonin reuptake inhibitor (SSRI) paroxetine and also those acting through other mechanisms involved in maintenance of the airway such as anti-cholinesterases, have had modest effects on overnight breathing in patients, but none so far has proved useful for daytime symptoms (Smith et al., 2006).

Parasomnias such as night terrors and REM behaviour disorders are rare; however, when injurious they do cause significant distress and their treatment is unsatisfactory. Both can be treated with high doses of clonazepam, a long-acting benzodiazepine which has significant daytime effects, and withdrawal can be problematic. Night terrors respond very well to SSRIs with the best evidence for paroxetine (Wilson et al., 1997), though none is licensed for this disorder. To our knowledge, no models currently exist for the non-REM parasomnias, but mechanisms have now come to light in rat models that could explain the pathophysiology of REM behaviour disorder and subsequent development of the associated neurodegenerative disorders, Parkinson's disease and dementia (Boeve et al., 2007). Modelling these disorders in animals or healthy volunteers presents a challenge, but is a clinical area where development of models is important.

Using sleep to measure serotonergic effect in the brain

The measurement of sleep architecture can give important insights into the action of agents which affect different receptor systems in the brain, such as serotonin. Since time of its discovery over 40 years ago, the serotonergic system has been implicated in the regulation of the sleep–wake cycle (Jouvet, 1969). Early studies in cats indicated that serotonin was associated with the initiation and maintenance of sleep, but later there were indications that serotonergic neurons also played a role in inhibiting sleep (for review see Jouvet, 1999). Subsequently it has been shown that these inconsistencies are due in part to the differential effect of serotonin on the sleep and wake-promoting centres of the hypothalamus and brain stem (Saper et al., 2005). Moreover, the multiple 5-HT receptor subtypes are differentially involved in the regulation of the different sleep states and sleep stages (Monti and Jantos, 2008).

One of the most consistent effects of pharmacological action on sleep architecture has been the robust and immediate suppression of REM sleep caused by administration of many antidepressant drugs, both in animals (monkey, Crofts et al., 1998; rat, Ivarsson et al., 2005; mouse, Monaca et al., 2003; cat, Sommerfelt and Ursin, 1991) and in healthy volunteers and depressed patients (Wilson and Argyropoulos, 2005). The effects are dose-related and consist of reduction in the overall amount of REM sleep during the sleep period, and delay of the first entry into REM sleep (increased ROL). REM-suppressing antidepressants include the SSRIs, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and the dual action reuptake inhibitors such as venlafaxine. The mechanism of REM suppression after SSRI administration may be mediated through the $5HT_{1A}$ receptor. This is based on preclinical studies (Monaca et al., 2003), showing that in $5HT_{1A}$ knockout mice the REM-suppressing effect of citalopram was absent, and in humans selective $5HT_{1A}$ agonist drugs are strongly REM suppressing (Wilson et al., 2005). The other types of antidepressant increase the levels of both serotonin and noradrenaline, and also dopamine in the case of the MAOIs (Wilson and Argyropoulos, 2005). The tricyclics have action at several other receptors, so their actions to suppress REM sleep may be through any of these. However, the utility of REM suppression as an index of serotonin function in the brain is supported by several studies. For example, decreasing serotonin availability by rapid tryptophan depletion in SSRI-treated depressed patients reversed the SSRI-induced REM suppression (Moore et al., 1998), and in patients chronically treated with the MAOI phenelzine where REM was markedly suppressed, tryptophan depletion reversed this effect (Landolt et al., 2003), indicating that the REM-suppressing effects are serotonergic in this antidepressant that increases multiple neurotransmitters. The REM sleep suppression seen acutely is maintained during chronic administration of SSRIs in depression, unlike the changes in sleep continuity described below.

Changes in sleep initiation and continuity after acute SSRIs are also similar in volunteers and depressed patients, and consist of an increase in light (stage 1) sleep, the number

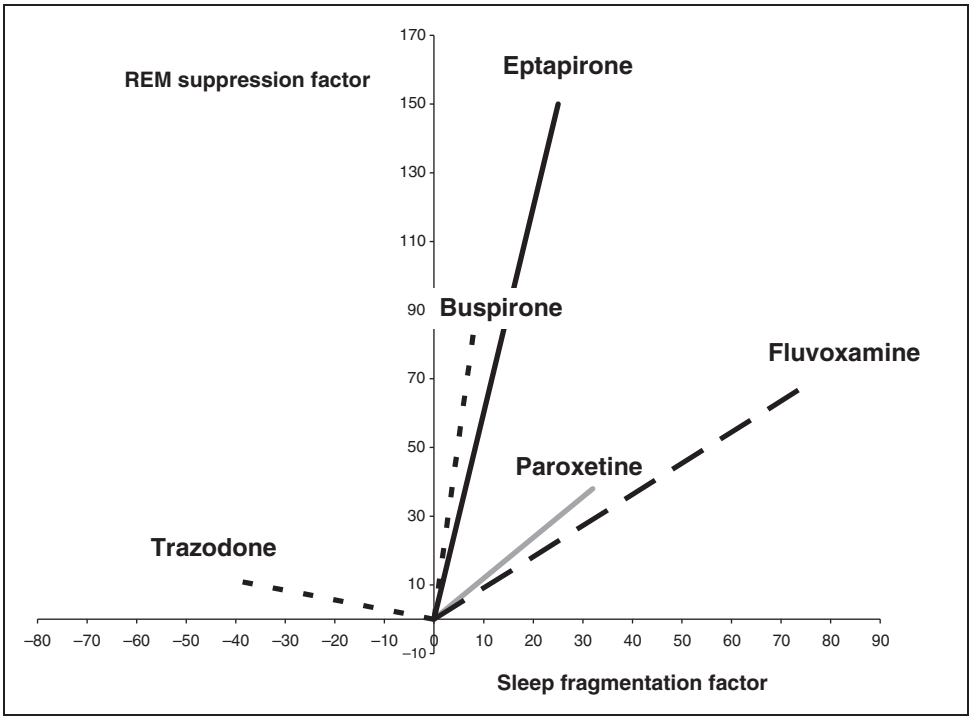

Figure 2. Sleep vectors; the relative REM suppressing and sleep fragmenting effects of serotonergic drugs. REM suppression factor = Reduction in amount of REM sleep (min) + increase of REM onset latency (min). Sleep fragmentation factor = reduction in total sleep time + increase in waking time + increase in stage 1 sleep time (minutes). Data are plotted so that the length of the derived 'vector' relates to the amplitude of the effect, and its direction to the relative weight of the REM or the sleep-disrupting effect. Original data are from Wilson et al., 2000 (fluvoxamine), Wilson et al., 2005 (buspirone and eptapirone), Paterson et al., 2009a (trazodone) and an unpublished study (paroxetine).

of arousals from sleep, and time spent awake at night. In general the magnitude of this arousing effect has been larger in normal volunteers. However, it must be remembered that there is a large baseline difference between these two groups, with depressed patients starting out with disrupted sleep as part of their disorder, therefore further deterioration in their sleep is less obvious. In general, these sleep fragmentation effects diminish over time, with most studies in depressed patients showing no difference from baseline after a few days of treatment with SSRIs.

Fragmentation of sleep is probably not explained by the stimulation of $5HT_{1A}$ receptors, since potent $5HT_{1A}$ agonists do not have such marked sleep-fragmenting effects as the SSRIs (Wilson et al., 2005). It may be that stimulation of post-synaptic $5HT_2$ receptors is involved; blocking these with non-selective 5-HT_2 receptor drugs such as ritanserin or trazodone and with selective 5-HT_{2A} antagonists such as eplivanserin (SR 46349B) improves sleep in a similar manner (Landolt et al., 1999; Viola et al., 2002; Walsh et al., 1998), whereas $5HT_2$ agonists such as mCPP are sleep-disrupting (Lawlor et al., 1991). Certain 5-HT_{2A} antagonists and inverse agonists are now under investigation for the treatment of sleep-maintenance insomnia (Al-Shamma et al., 2010; Monti, 2010; Teegarden et al., 2008).

One useful method of assessing the effect of serotonergic drugs on sleep is to compare sleep architecture after single-dose challenges in healthy volunteers. We have found it useful to visualize the drug effects by plotting their REM-suppressing capability against the effects on sleep fragmentation (Figure 2). Thus, the reduction in the amount of REM sleep together with the lengthening of REM onset latency are combined to make a REM suppression factor, and the reduction in total sleep time and increase in waking and stage 1 sleep are combined to make a sleep fragmentation factor. These are plotted so that the length of the derived 'vector' relates to the amplitude of the effect, and its direction to the relative weight of the REM or the sleep-disrupting effect. As can be seen from Figure 2, the SSRIs such as fluvoxamine and paroxetine have both marked REM-suppressing and sleep-fragmenting effects (Wilson et al., 2000), $5HT_{1A}$ agonists such as buspirone and eptapirone have marked REM suppression but little sleep fragmentation (Wilson et al., 2005), and trazodone has little or no REM suppression and negative sleep disruption as it improves sleep (Paterson et al., 2009c). This approach has also proved useful to compare the effects of two SSRIs on sleep, when length of vectors accorded with clinical effects (Wilson et al., 2004).

Conclusions

Sleep architecture shows clear homology between species and is also one of the most sensitive indices of drug effects in the brain. We believe, therefore, that sleep studies offer interesting options for translational medicine. First, the

translatability of sleep parameters in animal models and humans allows for more effective prediction of efficacy in the clinic. This can be applied to facilitate the investigation of brain mechanisms of sleep, and to drug discovery in the major sleep disorders. Examples of effective translation in sleep medicine have recently been demonstrated with the discovery of the orexinergic system as a target for sleep disorders and subsequent emergence of orexin antagonists as possible treatments, the probing of selective 5-HT_{2A} antagonists as possible treatments for insomnia, and the development of several translational models of sleep disturbance. In addition, combining sleep recording with early-phase studies (such as dose-ranging) of potential serotonergic agents in healthy volunteers is relatively inexpensive, and can provide important information above and beyond the sleep effects alone. Any effect on sleep architecture and/or sleep EEG could signify brain entry, and the specific sleep alterations observed can indicate which pharmacological mechanisms are involved in the response, as has been suggested for the serotonergic system. The continuing growth in research into the brain mechanisms of sleep and circadian biology is likely to increase our need for effective translational models that will progress basic findings into the clinic.

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Conflict of interest

David J Nutt has provided consultancy services to Pfizer, GSK, Novartis, Organon, Cypress, Lilly, Janssen, Lundbeck, BMS, Astra Zeneca, Servier, Hythiam, and Sepracor, received honoraria from Wyeth, Reckitt-Benkiser, Cephalon, received grants or clinical trials payments from MSD, GSK, Novartis, Servier, Janssen, Lundbeck, Pfizer, Wyeth, Organon.

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