To sleep, perchance....

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Introduction

Sleeping is easy for many of us; but for a surprisingly large minority, it is often rather more difficult. These unfortunates know from experience how debilitating a prolonged period of poor nights can be, affecting one's general health and ability to function effectively. Indeed, the extreme of total sleep deprivation appears to be lethal, at least for rats, possibly due to weakening of the immune system. In humans, too, the impact of poor sleep can be profound, and some reports suggest that individuals sleeping less than six hours per night have a 70% higher mortality rate. It seems that although people can become accustomed to having inadequate sleep over long periods of time, this is not the same as being adapted to it, and prolonged lack of sleep can have a variety of damaging effects.

The architecture of sleep

Sleep is not a homogeneous state of passivity; in fact, it follows a well-defined pattern or 'architecture'. In healthy adults, sleep onset occurs within 20 minutes of retiring. Initially sleep is of the non-rapid eye movement variety (NREM), which itself is split into four stages of successively deeper sleep characterised by different brain wave patterns. In addition, there are episodes of rapid eye movement (REM) sleep, in which the body's physiological parameters are more typical of the waking person (higher pulse, etc). Electroencephalogram (EEG) studies indicate fast alpha and beta waves in the waking state, which are replaced by slower theta and delta waves during sleep; the different sleep stages exhibit different combinations of these neuronal firing patterns.

The sleep architecture of a normal adult is composed of about 25% REM and 75% non-REM sleep. Stages 1-4 of NREM and one REM episode together form a cycle, lasting about 90-100 minutes, which is repeated regularly throughout the night. Earlier sleep cycles are characterised by relatively short REM periods and longer periods of deep sleep (Stages 3 and 4), while later cycles exhibit longer REM periods and shorter episodes of deep sleep. However the normal pattern of sleep architecture can be disrupted in various circumstances of disease or disability, leading to the variety of symptoms classified under the heading of insomnia. In addition, the architecture of sleep commonly changes as an individual ages, possibly as a consequence of the aging process itself rather than being due to discrete medical problems. Deep sleep periods may contract or cease altogether in the elderly, with consequences for their alertness and well-being during the day.

Biochemistry of sleep

Sleep regulation is mediated via a number of discrete areas (nuclei) of the brain, found in the cerebral cortex, thalamus, hypothalamus and brain stem, together being known as the reticular activating system. Of particular importance is the suprachiasmatic nucleus (SCN), a pair of small regions found in the hypothalamus; the SCN influences the pineal gland which produces the hormone melatonin, a key regulator of the sleep/wake cycle. The SCN itself lies close to the point where the optic nerves cross in the brain, and is influenced by signals (perception of light) from the retina. Hence people with total blindness often experience sleep disorders due to their retinal cells being unable to signal the detection of light.

Major neurotransmitters (chemicals which mediate neuronal activity) involved in the pathways feeding to and from the SCN include glutamate, neuropeptide Y, serotonin (5-hydroxytriptamine or 5-HT), and gamma-aminobutyric acid (GABA). Other physiologically relevant molecules include dopamine, acetylcholine, prostaglandin D2 (which induces sleep by inhibiting adenosine activity in particular regions of the brain), and prostaglandin E2 (which promotes wakefulness by stimulating receptors in the posterior hypothalamus). Clearly these neurotransmitters or their receptors may represent molecular targets which could be manipulated by pharmaceuticals to achieve a desired state of sleep or wakefulness. For example, it seems that activation of GABA receptors by GABA causes a state of sleepiness, due to inhibition of neural pathways involved in wakefulness. Therefore drugs which can mimic GABA in that they also stimulate the GABA receptor should help to induce sleep, and indeed such drugs include well-known sedatives such as benzodiazepines and barbiturates.

GABA is the major inhibitory neurotransmitter in the mammalian CNS, and mediates its effects through different classes of receptor termed $GABA_A$, $GABA_B$ and $GABA_C$. The $GABA_A$ receptor, which is targeted by drugs such as the benzodiazepines, is the most abundant of these. It is a ligand-gated ion channel, ie one of a group of molecules that is well-established as a class of 'druggable' targets (about a third of all marketed drugs target ion channels). Normally, interaction of GABA with $GABA_A$ opens the ion channel to chloride ions, which hyperpolarise the neuronal cell membrane thereby reducing the excitability of the neuron and reducing neuronal transmission. $GABA_A$ has not only a GABA-binding site but also a benzodiazepine-binding site, and benzodiazepine interactions at this site modulate the ion channel activity by enhancing the effect of GABA.

$GABA_A$ is composed mainly of four sub-unit types, alpha, beta, gamma and delta, which themselves are subdivided into various forms (alpha 1, alpha 2 etc). The various combinations of these subunit types give a great diversity of $GABA_A$ receptors, each of which is likely to have a subtly or markedly different physiological function. For example benzodiazepine receptors containing alpha 1 subunits (Type 1) are said to mediate hypnotic effects and receptors containing alpha 2 receptors (Type 2) are said to mediate anxiolytic effects. Hence drugs such as diazepam which non-selectively bind to a multiplicity of $GABA_A$ subtypes have a multiplicity of different physiological effects. This largely is the basis of the broad side effect profile of the benzodiazepines. More preferable is to identify drugs which bind very specifically to different $GABA_A$ subtypes, thereby affecting only sleep, and not (for example) convulsions or anxiety. For example, zolpidem is a molecule that is structurally unrelated to the benzodiazepines but which also binds to benzodiazepine receptors, and which is said to be specific to the Type 1 class of benzodiazepine

receptors in the brain, suggesting a favourable side effect profile compared to the benzodiazepines (which bind both to Type 1 and Type 2 receptors).

Insomnia

It is beyond the remit of this article to examine the various causes of insomnia, so we shall confine ourselves to classifying insomnia by symptom. There are at least two different forms of insomnia symptom: difficulty in falling asleep (sleep initiation insomnia) and difficulty in remaining asleep (sleep maintenance insomnia, which may include early morning awakening). Other classifications describe four basic types of insomnia, namely: difficulty in falling asleep; 1-2 long periods of wakefulness after falling asleep; frequent, short awakenings; and early morning awakening. Insomnia symptoms, however they are classified, may be transient (days), relatively short-term (less than a month) or chronic (a month or more) in nature.

Treatments for insomnia

Drugs that promote sleep from which an individual can be easily awakened are known as hypnotics. Sedatives and anxiolytics (drugs which calm the patient and reduce anxiety) may also have a hypnotic effect at higher doses. Not all hypnotics that facilitate sleep do so in a manner which restores the normal sleep architecture. For example, alcohol has well-known sleep-inducing properties, but tends to keep individuals in Stages 1 and 2, while preventing the onset of the deeper, more restorative Stages 3 and 4, and also preventing REM sleep. This is an important point for developers of new insomnia drugs – it is not just the length of sleep that is important, but also the quality of sleep in terms of restoration of normal sleep architecture. Other important factors include: the rapidity of sleep induction; safety of the drug in case of overdose; tolerance or abuse potential; and potential for withdrawal symptoms or rebound insomnia after discontinuation of treatment. Thus, a product for long-term administration should be free of side effects such as tolerance or addiction, and a product to allow patients to get back to sleep after early morning awakening should have a half life such that the patient can awake naturally after a short time without any 'hangover' effect (residual sleepiness) the next day.

The main groups of drugs used as hypnotics are the benzodiazepines, the barbiturates and the 'non-benzodiazepines'.

Barbiturates have been almost completely superseded by other classes of drug, due mainly to problems associated with their safety and addictive potential, and prescribing today appears to be largely limited to a (dwindling) population of elderly patients who have become dependent on the drug. Barbiturates tend to have long half-lives (eg phenobarbital has a half-life of over 24h) and do not promote normal sleep architecture (they decrease the duration of Stages 3 and 4 and of REM sleep).

Benzodiazepines belong to a class of well-known drugs which includes diazepam and midazolam. Different types of benzodiazepine have different half-lives (eg triazolam is eliminated in about 6 h, and flurazepam is eliminated in about 12 h). This has implications for the treatment of insomnia; if a patient with early morning awakening were to take a benzodiazepine with a 12h half-life, he would be unlikely to avoid a residual hangover effect the next day. Therefore, the short-half life benzodiazepines might be preferable; however, these are often associated with more severe withdrawal effects than their longer-half life cousins. In addition, benzodiazepines

have other side effects including alteration of sleep architecture (reduction of Stages 1, 3 and 4 and of REM phase sleep, increase of Stage 2) and tolerance/addiction.

Non-benzodiazepines appear to have fewer side effects than the benzodiazepines; they include zolpidem, zopiclone and zaleplon.

Zolpidem is an imidazopyrimidine with a short half-life of 2.5h. Studies appear to show that apart from reducing sleep latency and slightly increasing the duration of Stages 3 and 4 during the first 2 hours after sleep onset, zolpidem does not affect sleep architecture. Zolpidem does not cause rebound insomnia or withdrawal when administered at therapeutic doses. Zopiclone, a cyclopyrrolone, has a 5h half-life, and studies suggest no significant effect on sleep architecture.

Zaleplon, a pyrazolopyrimidine, has an even shorter half life (1h); but this may be a problem for some insomniacs in that the effect may wear off in the early hours of the morning. In general, studies appear to suggest that zaleplon has no significant effect on sleep architecture, and that it is not associated with rebound insomnia or withdrawal at normal doses.

All of these drugs appear to be improvements on the benzodiazepines. However, for many cases of insomnia, particularly sleep maintenance/early morning awakening, it may be that zolpidem has the most ideal half-life profile, being long enough to maintain sleep but short enough to avoid hangover effects the next morning. This, together with its favourable side-effect profile, probably accounts for the strong sales history of zolpidem products.

Waking up the market

Questioning of the general population tends to suggest that about 30-40% of us feel that we are not getting a good night's sleep. Even allowing for those who sleep like logs for eight hours but are apparently unaware of it, there would seem to be a significant percentage of the population that has some form of sleep disorder. The market for products that address these disorders therefore should be significant. Indeed, 2002 sales of one of the better-known insomnia treatments were in the region of $1200M, and there are said to be 25 million insomnia prescriptions per year in the US alone. Furthermore, these figures are achieved against a background of apparent under-treatment, as it is said that less than 5% of insomniacs actually seek help for their disorders. Effective products for insomnia therefore represent significant commercial opportunities, but achieving their full potential may require some clever marketing to flush out the silent sufferers. Comments should be directed to the author at nm01@beremans.com.