Insomnia: An Overview

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ABSTRACT

Chronic insomnia affects a significant proportion of young adults and elderly populations. Its effects are related not only social life but also the development of economy. Currently, scientists have revealed the sleep architecture and developed many strategies for treatment. Current pharmacological approaches focus primarily on Gamma Butyric Acid (GABA), the major inhibitory neurotransmitter in the central nervous system. In addition, other receptors, such as serotonin, histamine, melatonin, are also considered. In this review, we focus on sleep disorder, the sleep architecture and current treatment methods for sleep disorder.

Keyword: ***Insomnia, sleep disorder, GABA.***

1. Introduction for Insomnia

Insomnia is currently a widespread health complaint a drepresents the most common sleep disorder worldwide. Approximately 1 in 4 adults experiences insomnia at some time; at least 10% of the general population considers the problem to be chronic (Mendelson et al., 2004; Sateia & Nowell, 2004). Recent study in South Korea showed that 22.8% of the 5,000 adults complained of insomnia, with the prevalence being significantly higher in women (25.3%) than in men (20.2%) (Cho et al., 2009).

Insomnia was classified to several types, which are not mutually exclusive and include difficulty for initiating sleep (sleep-onset insomnia), frequent or long nighttime awakenings (sleep-maintenance insomnia), and waking up too early without being able to return to sleep (also sleep-maintenance insomnia). The type of insomnia can vary over time in any individual and is classified based on its duration (Hohagen et al., 1994). Acute insomnia lasts 1 to 3 nights, short-term

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insomnia lasts 3 nights to 1 month, and chronic insomnia lasts longer than 1 month. Acute insomnia is often caused by emotional or physical discomfort and, if left untreated, may develop into chronic insomnia (Krystal, 2005).

In addition, certain medical conditions are associated with an increased risk of insomnia (Roth, 2009). These include chronic pain, high blood pressure, gastrointestinal problems, urinary problems, osteoarthritis, hip impairment, fibromyalgia, peptic ulcer disease, and breathing problems (Ancoli-Israel, 2006; Katz & McHorney, 1998; Leigh et al., 1988; Taylor et al., 2007).

The potential negative effect that insomnia may have on health is further evidenced by its association with the increased risk of certain psychiatric and medical comorbidities, including anxiety and depression (Winokur et al., 2001), obstructive sleep apnea hypopnea syndrome (Smith et al., 2004), and alcoholism (Brower, 2003). Shorter sleep time is associated with impaired glucose regulation and with increased risk of diabetes (Gottlieb et al., 2005; Van Cauter & Knutson, 2008). (Fig. 1)

Moreover, Insomnia can affect daytime functioning by impairing one's ability to perform common tasks. Daytime sleepiness interfered significantly with daily activities. These daytime impairments are due to the negative effects of insomnia on memory, the ability to concentrate and focus, psychomotor function, and alertness. Such functional impairments can result in decreased productivity at home and at work (Chilcott & Shapiro, 1996). Decreased safety in the workplace is another consequence of daytime functional impairments resulting from insomnia. Workers with sleep disorder symptoms have a higher occupational injury rate than those without sleep problems (Nakata et al., 2005). In a Swedish study (Akerstedt et al., 2002), trouble in sleep was significantly associated with increased risk of fatal occupational accidents. Impaired performance due to reduced or inefficient sleep creates public safety risks when individuals with excessive daytime sleepiness are involved in potentially dangerous daily activities such as driving (Pandi-Perumal et al., 2006).

2. Sleep structure and function

Sleep in the normal adult is accomplished when a number of changes in the central nervous system (CNS) bring about a set of behavioral, physiological and psychological changes. It was reported that the putative roles of sleep in neural plasticity and memory consolidation, and in thermal and immune regulation (Rogers et al., 2001; Steriade, 2004; Baker et al., 2005; Walker, 2005). The Rechtschaffen and Kales system for scoring sleep stage (Rechtschaffen & Kales, 1968)

distinguishes a Wake state, nonrapid eyes movement (NREM) sleep, and rapid eyes movement (REM) sleep. REM and NREM sleep can clearly be differentiated on the basis of a number of physiological variables including muscle tone, elecroencephalogram (EEG) and electromyelographic (EMG) features, and the presence or absence of REM (Erman, 2001). Sleep is a continuous stage without clear transitions. However, for historical reasons it is staged as either REM or NREM stages 1–4 using visual scoring criteria that are based, in part, on the quantity and type of EEG waveforms per unit time. NREM stages 1 and 2 have been described as light sleep because of the relative sensitivity to acoustic stimuli characteristic of these phases of the sleep cycle, while stages 3 and 4 are often described as deep or slow wave sleep (SWS). The hallmark waveform of SWS consists of rhythmic, low frequency waves (~0.5–4.5 Hz). These electrical patterns also occur outside of stages 3 and 4 and are referred to as slow wave activity (SWA). The amount of SWA in the EEG can be quantified by application of the Fourier transform to the complex signal, providing another objective means of evaluating the sleep process.

Furthermore, in rodents, sleep stages are usually divided into REMS and NREMS. In NREMS, deep sleep dominated by delta wave (0.65–4 Hz); theta wave (6–10 Hz) and alpha wave (12–14 Hz) are related to light sleep and unconsciousness, respectively (Wafford and Ebert, 2008).

3. Role of GABA in sleep induction and maintenance

GABA is the major inhibitory neurotransmitter in the human central neural system (CNS), and GABAergic neurotransmission plays a key role in sleep regulation (Smith & Simpson, 2003). The fast inhibitory actions of GABA are mediated by the activation of $GABA_A$ receptor in the brain (Sieghart & Sperk, 2002). In the process, GABA induces membrane hyperpolarization by allowing chloride anion (Cl^-) influx (Fig. 3) (Jacob et al., 2008). As a result, neurotransmission is inhibited, and GABA subsequently produces sedative-hypnotic, anxiolytic, and anticonvulsant effects (Stephenson, 1995). $GABA_A$ receptor is a pentameric transmembrane protein consisting of 5 subunits that form a central anion channel. There are 19 different $GABA_A$ receptor subunits that have been identified and subdivided into 8 distinct groups: α1-6, β1-3, γ1-3, ρ1-3, δ, ε, π, and θ (Sieghart et al., 1999; Bateson, 2004). Most of $GABA_A$ receptors are composed of two α subunits, two β subunits, and one γ subunit (Whiting et al., 1999). $GABA_A$ receptors mediate a wide range of pharmacological effects including sedation, anxiolysis, and muscle relaxation due to the diversity of their subunit composition. The sedative-hypnotic effects of pharmacological compounds are mediated by $GABA_A$ receptors that contain α1 subunit (Molher, 2006). In addition,

$GABA_A$ receptors that contain α1 subunit constitute 60% of the $GABA_A$ receptor population and are distributed in the target areas of sleep-promoting pathway (Ebert et al., 2006; Molher et al., 2002; Pirker et al., 2000).

4. Current treatment methods

4.1.Benzodiazepine receptor agonists

Benzodiazepines are a class of chemically modulated GABA receptors. They bind to the GABA-A receptor and promote its inhibitory effects by causing conformational changes in the proteins that form channels through which chloride ions flow across neuronal membranes. The activity in GABAergic pathway involved to wake-promoting regions of the brain is thus increased, decreasing arousal and facilitating sleep (Sieghart & Sperk, 2002). The first benzodiazepine sedative, chlordiazepoxide, was developed and launched on the market in 1960 as Librium. The more potent diazepam Valium followed in 1960, and many other related benzodiazepines were subsequently launched (Chouinard, 2004). Several controlled trials have established the efficacy of benzodiazepines for the treatment of insomnia. Triazolam, temazepam, flurazepam, quazepam, and estazolam have been found to have beneficial effects on sleep onset and maintenance for patients aged 18 to 65 years with insomnia (Krystal, 2009). However, it was reported that benzodiazepines have addition effects beyond sleep enhancement, including next-day sedation, memory and cognitive impairment, anticonvulsant effects, and myorelaxation (Baker et al., 2004; Allison & Pratt, 2003).

4.2.Nonbenzodiazepines

Nonbenzodiazepines are chemically unrelated to benzodiazepines, but have similar effects by acting through related pharmacologic mechanisms. They bind to same site on the GABA-A receptor complex; however, the affinity is more specifically to subtypes of GABA-A receptors. Receptor binding affinities and *in vivo* in modulating the GABA response at different receptor subtypes vary among the nonbenzodiazepines class (Sanna et al., 20020. In addition, the nonbezodiazepine agents also differ in term of elimination half-life. All of these agents have shorter half-life than most benzodiazepines; therefore, they can be expected to be effective in facilitating sleep onset (Krystal, 2009). The side-effect profile of nonbenzodiazepines has been found to be similar to the benzodiazepines and includes sedation, dizziness, and psychomotor impairment. Nonbenzodiazepines appear to have lower abuse potential at recommended doses, but may still have a significant risk at higher doses (Griffiths & Johnson, 2005).

4.3.Melatonin receptor agonists

Melatonin is an endogenous hormone released from pineal gland during night that is involved in regulation of circadian rhythm in the brain. Low levels of melatonin have been linked to insomnia, and administration of melatonin is thought to be sleep promoting (Cajochen et al., 2003). However, melatonin has short half-life and high first-pass metabolism that limit in oral administration (Richey & Krystal, 2011). The most common side effects of melatonin are headache, sedation, and slowed reaction times (Graw et al., 2001; Dollins et al., 1994). In addition, it may have effect on fertility in both men and women (Ianas et al., 1999; Partonen, 1999). Another melatonin receptor agonist has been approved by FDA is ramelteon. Ramelteon has high affinity for MT1 and MT2 receptors located in SCN and recommended dose of 8 mg for patients with difficulty falling sleep [3(Borja & Daniel, 2006). Ramelteon also has some adverse effects, such as dizziness, nausea, and fatigue; however, there are no evidences about side effect on fertility have been reported (Kyger et al., 2007).

4.4.Antihistamines and antidepressants

Antihistamine is the class of agents that were developed for allergies treatment. However, it was reported that antihistamines could apply in treatment of mild insomnia. Diphenhydramine and doxylamine are commonly used in treatment of insomnia (Kudo & Kurihara, 1990). The common side effects of antihistamines are dry mouth, blurred vision, urinary retention, sedation, dizziness, weight gain, and delirium (Koppel et al., 1987).

Recently, antidepressants are developed in treatment of insomnia, such as trazodone, nefazodone (Krystal, 2009). These agents enhance sleep through antagonism of wake-promoting systems including serotonin, norepinephrine, and acetylcholine. Antidepressants are typically applied at lower doses for insomnia treatment than for the treatment of depression (Richardson & Roth, 2001).

5. Future prospects

Sleep disorder will effect to development of society. Current pharmaceutical industry is focusing on synthesis medicine. However, there are many scientists who focus on developing safety and health treatment methods from plants (Cho & Kim, 2013). Therefore, in research field of sleep effects, screening of binding or functional activity of marine plant extracts and compounds on various neurotransmitter receptors is the most important step. Natural products will become one of the major materials for developing sleep drugs in the future.

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