Alcohol 49 (2015) 299–310

Contents lists available at ScienceDirect

Alcohol

journal homepage: http://www.alcoholjournal.org/

Alcohol disrupts sleep homeostasis

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ARTICLE INFO

Article history:
Received 10 May 2014
Received in revised form
2 July 2014
Accepted 7 July 2014

Keywords:
Alcohol dependence
Adenosine
Basal forebrain
Binge drinking
Cholinergic
Sleep deprivation

ABSTRACT

Alcohol is a potent somnogen and one of the most commonly used "over the counter" sleep aids. In healthy non-alcoholics, acute alcohol decreases sleep latency, consolidates and increases the quality (delta power) and quantity of NREM sleep during the first half of the night. However, sleep is disrupted during the second half. Alcoholics, both during drinking periods and during abstinences, suffer from a multitude of sleep disruptions manifested by profound insomnia, excessive daytime sleepiness, and altered sleep architecture. Furthermore, subjective and objective indicators of sleep disturbances are predictors of relapse. Finally, within the USA, it is estimated that societal costs of alcohol-related sleep disorders exceeds $18 billion. Thus, although alcohol-associated sleep problems have significant economic and clinical consequences, very little is known about how and where alcohol acts to affect sleep. In this review, we have described our attempts to unravel the mechanism of alcohol-induced sleep disruptions. We have conducted a series of experiments using two different species, rats and mice, as animal models. We performed microdialysis, immunohistochemical, pharmacological, sleep deprivation and lesion studies which suggest that the sleep-promoting effects of alcohol may be mediated via alcohol's action on the mediators of sleep homeostasis: adenosine (AD) and the wake-promoting cholinergic neurons of the basal forebrain (BF). Alcohol, via its action on AD uptake, increases extracellular AD resulting in the inhibition of BF wake-promoting neurons. Since binge alcohol consumption is a highly prevalent pattern of alcohol consumption and disrupts sleep, we examined the effects of binge drinking on sleep-wakefulness. Our results suggest that disrupted sleep homeostasis may be the primary cause of sleep disruption observed following binge drinking. Finally, we have also shown that sleep disruptions observed during acute withdrawal, are caused due to impaired sleep homeostasis. In conclusion, we suggest that alcohol may disrupt sleep homeostasis to cause sleep disruptions.

Published by Elsevier Inc.

Introduction

Since the dawn of civilization, humankind has used alcohol for various reasons, including as a relaxant and for euphoric effects. Although the word "alcohol" in organic chemistry refers to any organic compound where the carbon atom of an alkyl group or a substituted alkyl group is bound to a hydroxyl group (−OH). However, in normal usage, the word *alcohol* is commonly used to describe ethanol or any beverage that contains alcohol. Alcohol is among the most highly abused drugs worldwide and a leading preventable cause of premature disability and death, accounting for an estimated 6–9% of all deaths (Rehm et al., 2009; Shield et al., 2013).

Alcohol is a potent somnogen and has a profound impact on sleep (Fig. 1). Acute alcohol intake, in non-alcoholic social drinkers, reduces the time to fall asleep (sleep onset latency); consolidates and enhances the quality (delta power) and the quantity of NREM sleep. It is this sleep-promoting characteristic of alcohol that makes it one of the most commonly used "over the counter" sleep aids (Johnson, Roehrs, Roth, & Breslau, 1998; Roehrs & Roth, 2001, 2012). However, alcohol-induced sleep promotion is short-lived and sleep is severely disrupted during the second half of the night.

Alcoholics also suffer from severe and protracted sleep disruptions manifested by profound insomnia, excessive daytime sleepiness, and altered sleep architecture (Brower & Perron, 2010; Colrain, Turlington, & Baker, 2009). Furthermore, subjective and objective indicators of sleep disturbances are predictors of relapse (Brower & Perron, 2010). Finally, within the United States, it is estimated that the cost of alcohol-related problems exceeds $180 billion, out of which more than $18 billion is associated with alcohol-related sleep disorders. Thus, although alcohol-associated sleep problems have a

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http://dx.doi.org/10.1016/j.alcohol.2014.07.019
0741-8329/Published by Elsevier Inc.

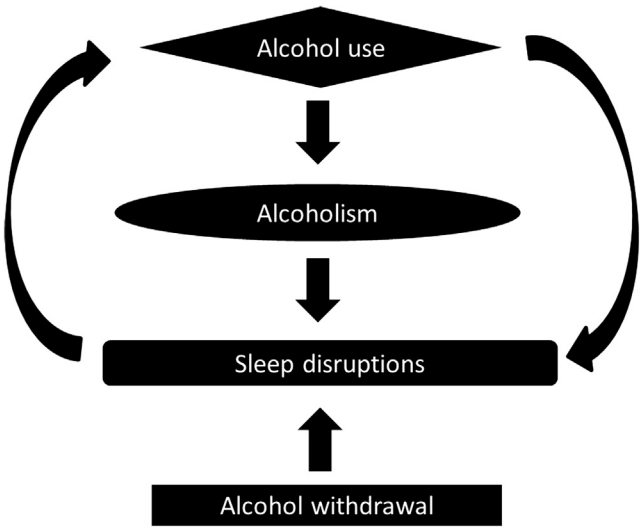

Fig. 1. Alcohol has complex interactions with sleep.

significant socio-economic impact on the individual, the individual's family and society, very little is known about how and where alcohol acts to affect sleep.

About 5 years ago, we started our research program to understand the mechanisms mediating the effects of alcohol on sleep-wakefulness. In this review, we have described what we have uncovered about how and where alcohol acts to affect sleep.

To understand the neuronal substrates responsible for mediating the effects of alcohol on sleep, it is essential to understand how sleep is regulated. Therefore, we will begin this review by describing the fundamentals of sleep regulation, followed by a description about the effect of alcohol on human and animal sleep. Finally, we will provide a summary of our published as well as unpublished/preliminary findings.

Fundamentals of sleep

Sleep is an immense topic. It is difficult to describe sleep in a few paragraphs. In this section, we have attempted to provide some fundamentals. An interested reader is recommended to some excellent reviews (Brown, Basheer, McKenna, Strecker, & McCarley, 2012; Datta & Maclean, 2007; McCarley, 2007; Rosenwasser, 2009).

Sleep has always fascinated humankind. There is a myriad of treatises and reviews, scientific and non-scientific, trying to explain the phenomenon of sleep, yet none have been comprehensive enough to gain general acceptance. It is now well established that sleep is neither a unitary nor a passive process. Rather, intricate neuronal systems via complex mechanisms are responsible for the initiation and maintenance of sleep.

Sleep is defined as a rapidly reversible state of immobility and greatly reduced sensory responsiveness (Campbell & Tobler, 1984). An additional important criterion that is included in the definition of sleep is that sleep is homeostatically regulated, i.e., lost sleep is made up with an increased 'drive' for sleep and a consequent 'sleep rebound' (Campbell & Tobler, 1984).

Sleep is not a homogenous state. Rather, it is a continuum of states. The different components of the sleep continuum in mammalian species could broadly be divided into two major states: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. A combination of electrophysiological measurements including 1) electroencephalogram (EEG), which traces the electrical activity of the brain, 2) the electro-oculogram (EOG), which measures eye movements, and 3) the electromyogram (EMG), which measures the electrical activity of muscles, is used objectively to identify different stages of the sleep-W cycle (Datta & Maclean, 2007).

Physiology of sleep

The state of active wakefulness is characterized by the presence of low-voltage, high-frequency (>15 Hz) waves in the EEG, REMs in the EOG, and high-amplitude activity in the EMG. In humans, NREM sleep is divided into three stages.

Stage I is characterized by relatively low-voltage, mixed-frequency activity (3–7 Hz) and vertex sharp waves in the EEG.

Stage II is characterized by slow (<1 Hz) oscillation with distinctive sleep spindles (waxing and waning of 12–14-Hz waves lasting between 0.5 and 1.0 s) and K-complex waveforms (a negative sharp wave followed immediately by a slower positive component).

Stage III (also termed as slow-wave sleep) is characterized by the dominance of high-amplitude, low-frequency (<4 Hz) waves in the EEG. This state is the deepest stage of NREM sleep.

In laboratory animals (cats, rats, and mice), NREM sleep is generally not subdivided into stages. It is identified by the presence of high-amplitude, low-frequency waves in the EEG.

REM sleep is characterized by an ensemble of concomitant events including: 1) low-amplitude and high-frequency waves in the EEG; 2) very low or complete absence of activity in the EMG (muscle atonia), and 3) singlets and clusters of rapid eye movements (REMs) in the EOG. Supplemental to these polysomnographic signs, other REM sleep-specific physiological signs in mammals are 1) phasic ponto-geniculo-occipital (PGO) activity, 2) tonic hippocampal theta activity, 3) myoclonic twitches, most apparent in the distal limb musculature; 4) pronounced fluctuations in cardio-respiratory rhythms and core body temperature, and 5) penile erection and clitoral tumescence.

In adult humans and non-human primates, circadian distribution of the sleep period is mainly monophasic. While NREM sleep occupies the majority of time during the first half of sleep time, REM sleep is predominant in the second half.

In laboratory animals (mouse, rat, and cat), circadian distribution of the sleep period is polyphasic and the NREM-REM sleep cycles are shorter and continue throughout sleep periods during day and night.

Cellular substrates of sleep-wakefulness

Multiple neuronal systems contribute to the promotion and maintenance of the awake state, which is characterized by cortical activation and behavioral arousal. Using predominantly glutamate as the neurotransmitter, neurons within the brainstem reticular activating system (RAS), via two major ascending relays, control cortical activation that occurs during wakefulness and REM sleep [Fig. 2; Brown et al., 2012; Jones, 2005].

The ventral relay from the RAS is the major pathway controlling cortical activation. This relay system consists of the ascending fibers from several brainstem nuclei, including noradrenergic locus coeruleus (LC), serotonergic raphe system (DRN) and via the medial forebrain bundle, pass through and/or synapsing with several wake-promoting centers including the histaminergic tuberomammillary (TMN) and the orexinergic perifornical hypothalamus, and project to the basal forebrain (BF). The BF, in turn, projects to and controls the activation of the cortex (Brown et al., 2012; Datta & Maclean, 2007; Jones, 2003; Thakkar, 2011).

The dorsal relay of the RAS includes the mesopontine cholinergic neurons localized in the pedunculopontine and laterodorsal