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Alcohol use and abuse: Effects on the brain sleep-controlling mechanisms and sleep health

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Abstract

Alcohol or ethanol is a widely used psychoactive substance in India, and its abuse is a significant public health concern. Sleep is a homeostatic behavior that is essential for physical and mental well-being. Chronic sleep disturbance negatively affects the body's physiology and has been associated with a number of adverse health outcomes. These include obesity, type-2 diabetes, cognitive decline, cardiovascular disease, and neuropsychiatric disorders. Although mainly used on social occasions, alcohol is often used to self-medicate for insomnia and stress. Findings from human and animal studies support that although alcohol ingestion acutely induces rapid sleep onset, it eventually causes, especially its chronic use, significant sleep disturbance and contributes to poor quality of sleep quality. This review discusses the relationship between alcohol consumption and sleep disturbance. We provide an overview of: a) the prevalence of alcohol use and abuse in India; b) the features/architecture of natural sleep and brain circuitry and mechanisms of sleep regulation; c) how alcohol affects natural sleep; d) the molecules and potential brain targets where alcohol act to produce sleep disturbance; and e) the mechanisms that underlie detrimental effects of alcohol on sleep health.

Keywords: Ethanol, alcohol, sleep, sleep disturbance, insomnia, brain, hypothalamus

1. Introduction

Alcohol is a broad term that refers to a group of organic compounds that contain a hydroxyl (-OH) group attached to a carbon atom. Ethanol is the most common and the type of alcohol found in alcoholic beverages. Other types of alcohol include methanol, isopropanol, and butanol. Alcohol has a wide range of uses and applications. However, alcoholic beverages are consumed for their psychoactive effects, as they can alter mood, behavior, and perception.

Alcohol is one of the most used psychoactive substances in India and the world ^[1]. Although alcohol is commonly used on social occasions, it is often consumed for insomnia, stress, and anxiety relief. While India has one of the lowest per capita alcohol consumption rates in the world, the harmful effects of alcohol are still a significant public health problem (1). According to a study, alcohol consumption in India increased by 55% from 2005 to 2016, with a substantial rise in heavy episodic drinking among men and women ^[2]. The study also found that alcohol use was responsible for more than 5% of all deaths in India in 2016, with the majority of these deaths attributed to liver disease, road traffic accidents, and cancer. Alcohol use is not only a significant risk factor for death and disability but is also a major cause of domestic violence in India ^[3]. Furthermore, alcohol use disorders are associated with several mental health problems, including depression and anxiety. Also, most alcoholics smoke, another commonly used and abused psychoactive substance worldwide, further increasing health hazards. Tobacco and nicotine use increases alcohol craving, decrease the effects of alcohol, and thus further increases alcohol consumption ^[4].

The government has carried out several policies to regulate alcohol consumption, including raising the minimum age for drinking and increasing taxes on alcohol. However, the enforcement of these policies has been inconsistent and not very successful in curbing the use of alcohol in India. The availability/accessibility of alcohol also varies widely across different regions of the country, with some states, including Bihar imposing complete prohibitions on alcohol consumption. The patterns of alcohol use in India also differ between men and women, with men more likely to consume and engage in heavy drinking.

Sleep is a physiologically complex and essential homeostatic behaviour observed throughout the animal kingdom, from flies to humans. Nearly seven h of sleep (~30% of our life) is needed for a human adult's physical and mental health. On the other hand, chronic sleep

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disturbance is associated with several adverse effects on health, including cognitive decline, anxiety, cardiovascular disease, and neuropsychiatric disorders, all contributing to poor quality of life [5-6].

While alcohol may have some positive effects in moderation, findings from various studies suggest that excessive or chronic alcohol consumption may adversely affect physical and mental health. One such adverse consequence is sleep disturbance. This review will examine the relationship between alcohol and sleep disturbance. We especially aim to provide an update on.

- a) The features of natural sleep.
- b) Brain circuitry and neuronal mechanisms of sleep onset and control.
- c) Our current understanding of how acute and chronic alcohol consumption affects sleep architecture and the underlying mechanisms involved.

2. Sleep regulatory systems

A night of healthy sleep is essential for physical restoration and growth. A lack of sleep can lead to fatigue, impaired concentration, decreased immune function, and various adverse health outcomes. For a better understanding of the effects of alcohol on sleep, it is vital first to understand the typical sleep architecture and the mechanisms that underlie sleep regulation in normal healthy subjects.

2.1. Features of sleep

Mammalian sleep, including humans, is a complex state consisting of two alternating and distinct stages: non-rapid eye movement (NREM) sleep and REM sleep [7-9]. This classification is mainly based on three objective parameters, called electroencephalogram or recording of cortical waves; electromyogram (EMG) or recording of muscle tone; and electrooculogram (EOG) or recording of eye movements. Briefly, in the human adult, NREM sleep constitutes 75-80% of sleep and is characterized by electroencephalogram (EEG) synchronization and slow wave EEG activity called delta wave (0.5–4 Hz), and slowing down or absence of muscle tone (EMG) and eye movement (EOG). REM sleep occurs after the first 60-90 minutes of NREM sleep and is characterized by high frequency and low amplitude EEG waves, frequent eye movements, and loss of muscle tone. Similar sleep cycles occur repetitively throughout the night. However, as the night progresses, each cycle contains less NREM sleep and more REM sleep.

2.2 Sleep regulatory structures in the brain

In the brain, well-characterized sleep and wake-regulatory centers and the circadian clock are involved in the timely onset and regulation of sleep.

Various studies, including lesion, stimulation, neuro-imaging, and molecular studies, suggest that sleep-regulatory structures are present throughout the brain [7, 9-12]. However, a large body of studies supports that the preoptic/hypothalamic area (POA-AH), plays a critical role in sleep control (Brown *et al* 2012; Datta & Maclean 2007; Saper *et al* 2010). POA-AH lesions decrease sleep, whereas its activations increase sleep [13]. Insomnia caused by POA-AH lesions is attenuated after the transplantation of fetal POA tissue into the damaged POA [14]. The POA-AH contains several nuclei that are involved in sleep regulation. One of the critical nuclei in the POA-AH and a vital component of the brain's sleep-promoting system

is the ventrolateral preoptic nucleus (VLPO) [10, 15-16]. Studies have demonstrated that electrical stimulation of the VLPO promotes sleep, whereas its lesions disrupt sleep in animals. The POAH contains neurons that become activated before the occurrence of sleep and remain active during sleep [17, 18]. These are called sleep-active neurons; evidence suggests they play a role in sleep regulation. The POAH sleep-active neurons contain the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and project to several wake-promoting systems. Thus, when active, sleep-active POA-AH neurons inhibit wake-promoting systems promoting sleep [7, 9, 19].

2.3 Wake-regulatory Systems in the brain

The wake-promoting system, which promotes EEG desynchronization and behavioral arousal, consists of a diverse group of neuronal systems localized in the brainstem and hypothalamus. These include neurons containing the neurotransmitter.

- a) Monoamines, e.g., noradrenergic, serotonergic, dopaminergic, and histaminergic neurons in the brainstem and posterior hypothalamus.
- b) Acetylcholine in the brainstem and basal forebrain.
- c) Hypocretin-(orexin-) containing neurons in the perifornical-lateral hypothalamus [7, 9, 10, 20, 21].

2.4 Suprachiasmatic nucleus (SCN) and sleep- and wake-regulatory systems

Localized in the hypothalamus, SCN is the body's "master clock," controlling the circadian rhythms that govern our sleep-wake cycles. The SCN receives input from the eyes, which allows it to synchronize the body's circadian rhythms with the natural light-dark cycle. The SCN determines when it is appropriate for the body to sleep based on the light-dark cycle, while the VLPO promotes sleep by inhibiting wake-promoting brain areas. Together, these regions ensure that the body remains synchronized with the natural day-night cycle and that sleep occurs at the appropriate time [22, 23].

2.5 Sleep-onset and maintenance: mechanisms

According to a well-accepted hypothesis, POA-AH sleep-active neurons become active in response to circadian and homeostatic signals, including sleep factors, e.g., adenosine, nitric oxide, and interleukin-1 beta produced during wakefulness, causing sleep-onset or transitioning from waking to waking NREM sleep [24-26]. Please see Figure-3 A and B for details. The activated POAH sleep-promoting system inhibits wake-promoting systems, including monoamine, serotonin, histamine, and hypocretin systems, all involved in wake-promotion [9, 10, 27, 28]. Dysfunction of the POA-AH has been implicated in sleep disorders, including insomnia and sleep disturbance in aging, highlighting the role of this brain region in regulating and maintaining healthy sleep.

3. Alcohol and Sleep

Alcohol is a depressant of the nervous system. It slows down brain activity and causes sedation. This is why people often report feeling relaxed and drowsy after drinking alcohol, and people often consume alcohol to relieve stress, anxiety, and insomnia. However, while alcohol can help people fall asleep faster, it also disrupts the normal sleep-wake cycle [29-31]. Please see Figures 1 and 2 for details. The extent and nature

of sleep disturbance caused by alcohol also vary depending upon the amount and timing of its consumption. For example, consuming large amounts of alcohol shortly before bedtime is more likely to disrupt sleep than consuming small amounts earlier in the afternoon/evening. Individual differences in alcohol metabolism and tolerance can also impact the extent of sleep disturbance caused by alcohol [32-33].

3.1 Effects of the acute use of alcohol on sleep

1. 1-3 hours before bedtime

Much evidence supports that alcohol ingestion by healthy non-alcoholics 1-3 hours before bedtime significantly affects sleep architecture (33-35). The initial sleep-wake changes caused by alcohol include:

- A significant decrease in sleep latency;
- An increase in the time spent in NREM sleep;
- An increase in EEG delta power or slow-wave activity in NREM sleep, a measure of sleep depth or quality; and
- A decrease in the time spent in REM sleep.

However, changes in sleep-wake architecture that occur during the second half of the night include:

- Increased transitioning between sleep stages or sleep instability due to increased wakefulness, and
- Increased time spent in REM sleep and vivid dreaming.

These changes in sleep-wake parameters suggest that after alcohol intake, a person falls asleep much faster and experiences improved sleep to some extent. However, sleep quality worsens and becomes much more fragmented due to frequent arousal, frequent transitioning between sleep and wake stages, and increased vivid dreams during the second half of the night.

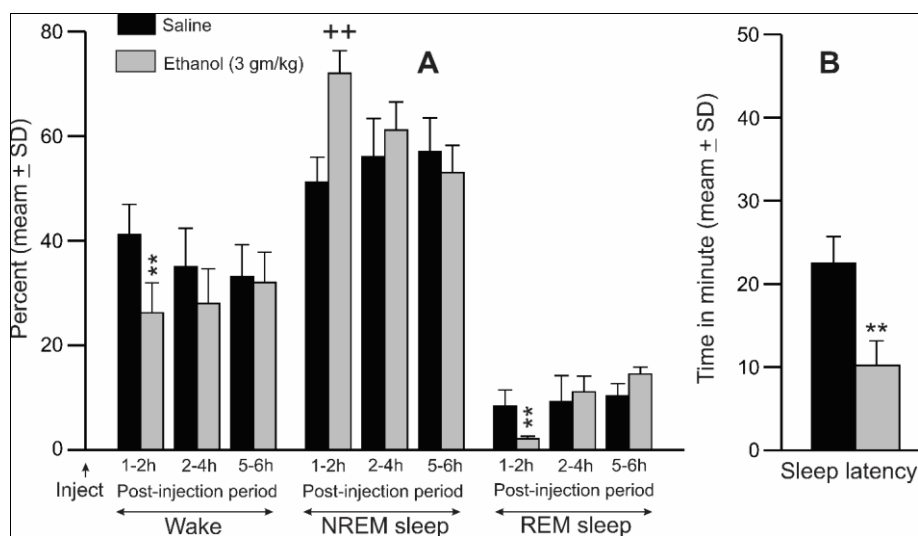


Fig 1: Effects of alcohol on sleep-wakefulness

- Bar diagrams show the amount (%) of wakefulness, NREM sleep, and REM sleep during the 6-hour post-injection recording period after saline and alcohol (ethanol) treatments. As compared to saline control, alcohol-treated animals exhibited decreased wakefulness, increased NREM sleep, and decreased REM sleep during the first 2 hours of the post-injection period.
- Bar diagram shows sleep latency after saline and ethanol treatments. After alcohol treatment, sleep latency decreased significantly, i.e., animals entered into sleep must faster than those treated with saline. *, decrease, **, $p < 0.01$; +, increase, ++, $p < 0.01$. Adopted from Alam and Sinha (2017), International Journal of Fauna and Biological Studies, 4: 05-11

2. 6 hours before bedtime

Alcohol ingestion, even six hours before bedtime or in the late afternoon, disrupts sleep at night. These effects include:

- A decrease in sleep efficiency or the ratio of the total time spent asleep compared to the total amount of time spent in bed during the night, and
- decreases in total sleep amount as well as REM sleep in the first half of the night.

- Increased bouts of waking and NREM sleep disturbance, especially in deep NREM sleep, in the second half of the night.

Alcohol ingestion also increases respiratory disturbances during sleep, which may worsen sleep disturbance after alcohol consumption. Alcohol consumption can lead to sleep apnea, a condition where the individual's breathing repeatedly stops and starts during sleep. This is because alcohol relaxes the muscles in the throat and can cause the airway to collapse or narrow, leading to breathing difficulties during sleep at night (29). This nighttime sleep disturbance may contribute to daytime sleepiness and cognitive impairment the following day. Studies also suggest that individuals who consume excessive amounts of alcohol are more likely to experience sleep apnea than individuals who do not drink alcohol or who consume alcohol in moderation.

3.2 Effects of long-term use of alcohol on sleep

Several studies suggest that, unlike occasional consumption by non-alcoholics, in individuals with alcohol use disorder, sleep remains quite disrupted (32). Individuals with alcohol use disorder exhibit:

- Increased sleep latency.

- b) Decreased sleep efficiency.
- c) Disrupted sleep, with decreased REM sleep and increased light NREM sleep.
- d) Increased wakefulness during the night.

These individuals also exhibit increased daytime sleepiness. The sleep-wake architecture in individuals with alcohol use disorders suggests that chronic alcohol use not only decreases sleep amounts at night but also alters the standard circadian patterns of sleep pressure. This potentially is caused due to the sedative effects of consuming large amounts of alcohol or as a consequence of severe sleep fragmentation or chronic sleep loss after alcohol consumption at night [36].

3.3 Effects of alcohol withdrawal on sleep

Alcohol withdrawal syndrome (AWS) is a set of symptoms that can occur when an individual who is addicted to alcohol suddenly stops drinking. One of the common symptoms of AWS is sleep disturbances. A study also found that the severity of AWS and the severity of sleep disturbances go hand in hand [37]. Alcoholics experience much severe consequences of withdrawal during the early withdrawal period, i.e., during the first and second weeks of abstinence

[36, 38]. The adverse effects include:

- a) Insomnia with long sleep latencies.
- b) Frequent occurrence of waking from sleep and shifts between different stages of sleep.
- c) A significant decrease in the deep NREM sleep, although overall NREM sleep amount may increase.
- d) Phase advance in REM sleep. Studies suggest that AWS is also marked by increased REM sleep, especially during the first two-thirds of the night, instead of the last third of the night, as in healthy subjects. Because of this increase in REM sleep, many alcoholics experience vivid dreams and nightmares.
- e) Hallucinations experienced by many alcoholics during withdrawal [39].

Evidence suggests that some individuals with alcohol use disorder may resume drinking to relieve their sleep disturbance and continued insomnia. In addition, individuals who experience alcohol withdrawal may be at increased risk of developing long-term sleep disorders. Studies also suggest that individuals with a history of alcohol use disorders are more vulnerable to developing insomnia and sleep apnea, even after extended periods of abstinence [40].

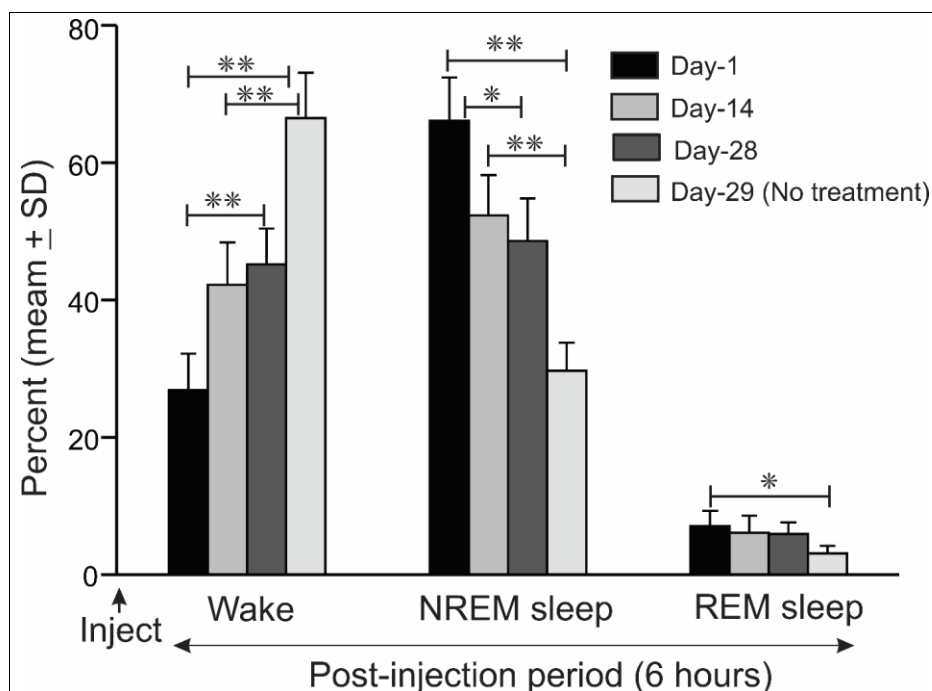


Fig 2: effects of chronic alcohol use on sleep-wakefulness. Bar diagrams showing wake, NREM sleep, and REM sleep amounts on days 1, 14, 28, and 29 during the 6 hours of recording after alcohol treatments. Alcohol increased sleep acutely (day-1), an effect that declined progressively with chronic treatments (days 14 and 28). Alcohol withdrawal on day-29 caused severe sleep disruption as indicated by increased waking and decreased nonREM and REM sleep. *, $p < 0.05$; **, $p < 0.01$. Adopted from Alam and Sinha (2017), International Journal of Fauna and Biological Studies, 4: 22-28

Animal studies

The effects of acute as well as chronic use of alcohol and its withdrawal on sleep are shown in Figures 1 and 2. Evidence from animal studies also suggests that treatment of alcohol acutely reduces sleep latency, increases NREM sleep and SW activity, and decreases REM sleep for about 3–6 hours, after which there are increases in wakefulness and rebound in REM sleep [33, 41]. On the other hand, 4-6 weeks of alcohol ingestion increases wakefulness and decreases NREM sleep and REM sleep during the day and decreases wakefulness and increases NREM sleep during the night. These changes indicate that

chronic alcohol consumption alters the circadian distribution of sleep and wakefulness. Like humans, increases in wakefulness and REM sleep and reductions in total sleep time and delta activity have also been reported in rodents with chronic alcohol use and during the withdrawal period [33, 42].

3.4 Neuronal mediators of alcohol-induced sleepiness and sleep disturbances

Alcohol is a simple compound that interacts with target cells mainly through hydrogen bonding, weak hydrophobic interactions, and specific neurotransmitter receptors. Thus, its

higher concentrations are needed for reinforcing and sedative effects [32, 43]. Alcohol passes from the digestive tract into the blood vessels and reaches the brain quickly. Within the brain, alcohol affects most neuronal systems via a combination of mechanisms ranging from altering neuronal membrane properties, affecting various enzymes, or directly affecting several neurotransmitter systems, including GABA, glutamate, dopamine, and serotonin [32, 43, 44, 45]. Here, we discuss neuronal groups and the mechanisms that may be responsible for the initial sleep-promoting effect of ethanol but eventually sleep disturbances due to its chronic use.

i) Mechanisms underlying acute effects of alcohol Consumption

Evidence suggests that alcohol interacts with many neurotransmitters/neuromodulators and potentially acts at multiple sleep and wake regulatory systems to produce its acute sleep-promoting effects [32-34]. Some notable of them include:

1. Gamma-aminobutyric acid (GABA)

GABA is an inhibitory neurotransmitter. The POA-AH sleep-active neurons predominantly contain the inhibitory neurotransmitter GABA. When activated, these neurons inhibit wake-promoting systems in the hypothalamus and brainstem via GABA release on those sites to produce sleep. Acute alcohol consumption likely amplifies GABAergic inhibitory tone on wake-promoting neurons by enabling the ion channel to stay open longer, thus letting more Cl⁻ ions into the cell. As a result, there is a general slowdown of wake-promoting systems and rapid onset of sleep after acute alcohol consumption in non-alcoholics.

2. Glutamate

In the brain, glutamate is the most abundant excitatory neurotransmitter, and most wake-active neurons contain glutamate. Alcohol inactivates several glutamate receptors, including *N*-methyl-D-aspartate (NMDA), L- α -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA), and kainate, which further potentiates the ability of alcohol to promote sleep. Histamine is another neurotransmitter involved in wake control. Evidence suggests this system also influences alcohol-induced sleep-wake changes and alcohol dependence. In alcohol-drinking rodent models, histamine receptor antagonists have been shown to reduce alcohol drinking and alcohol-induced place preference [33, 45].

3. Adenosine

Various lines of studies support that adenosine may play a critical role in mediating the effects of alcohol on sleep [46]. Adenosine promotes sleep by inhibiting wake-promoting systems, and alcohol acutely increases adenosine production in those regions, thus causing the acute hypnotic effects of alcohol [47-48]. Systemic administration of alcohol acutely:

- i. Increases extracellular adenosine levels in wake-regulatory regions.
- ii. Suppress the activity of wake-active neurons in those regions.
- iii. That blockade of adenosine receptor in those regions attenuates the sedative effects of alcohol [49, 50]. Caffeine is a nonspecific adenosine receptor antagonist that prevents sleepiness and improves alertness after alcohol ingestion.

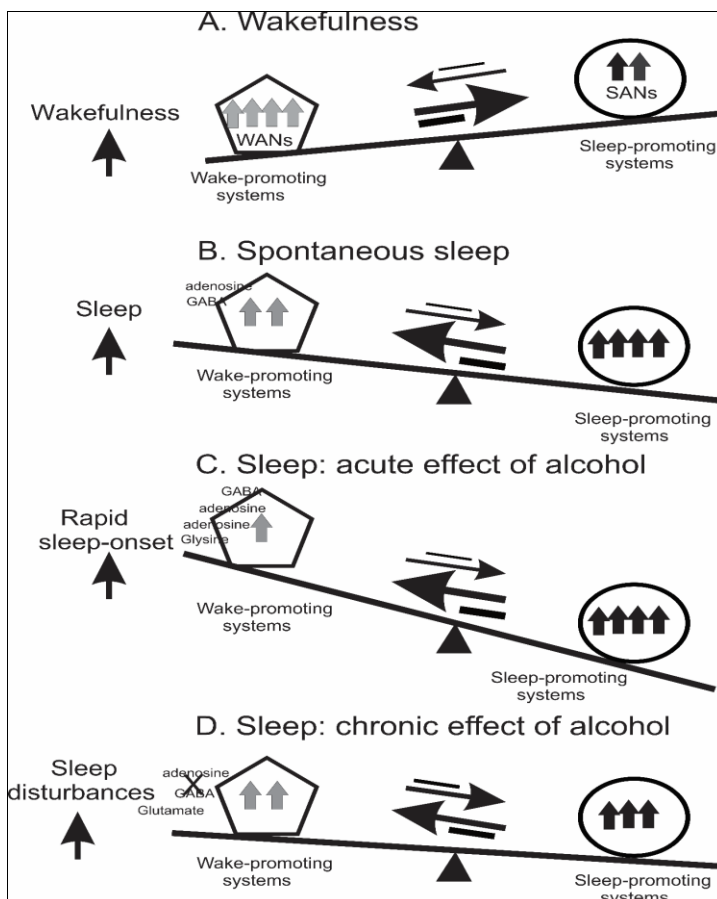


Fig 3: A simplified schematic representation of reciprocal interactions between sleep and wake regulatory systems.

This schematic diagram shows how mutually inhibitory interactions between wake- and sleep-regulatory systems cause the onset of sleep and waking and how alcohol may affect these systems to cause rapid onset of sleep after acute alcohol intake and sleep disturbances after chronic alcohol consumption. The thick and thin arrows with (-) indicate the magnitude of the inhibitory influence, and arrows in the sleep- and wake-regulatory systems represent the magnitude of activation of sleep- and wake-promoting neurons, respectively. A more robust activation of sleep-active neurons in combination with the inhibition of wake-promoting systems would cause rapid and consolidated sleep. However, even with strong activation of sleep-active neurons, a mild activation of wake-regulatory systems would cause sleep disturbances, which is observed during chronic alcohol consumption or during withdrawal. WANs, wake-active neurons; SANs, sleep-active neurons. For details, please see the text.

4. Glycine

Glycine is an amino acid that acts as an inhibitory neurotransmitter and is critical in regulating brain function. Studies have shown that acute alcohol consumption increases glycine release in the brain, leading to an increase in inhibitory activity. This effect potentially contributes to the sedative and anxiolytic effects of alcohol. However, chronic alcohol consumption can decrease brain glycine levels, which may contribute to the development of alcohol dependence and withdrawal symptoms.

Alcohol also affects the brain's reward system by increasing the release of dopamine, which can contribute to feelings of pleasure and euphoria. However, chronic alcohol consumption can lead to changes in dopamine signaling, contributing to addiction and dependence [32, 51].

Alcohol affects the serotonin system in the brain, which can contribute to its effects on mood and behavior. Alcohol can increase the release of serotonin, which can contribute to feelings of well-being and relaxation. However, chronic alcohol consumption may adversely affect the serotonergic system, contributing to depression and anxiety [52].

Overall, alcohol has complex effects on the brain, affecting multiple neurotransmitter systems that contribute to its sedative, rewarding, and mood-altering effects.

ii) Mechanism underlying chronic effects of alcohol consumption

Despite the initial sedative effects, regular and long-term alcohol consumption causes disruptions in sleep-wake patterns. The sleep-wake disturbance during repeated and chronic alcohol use and the withdrawal state following discontinuation are caused by adaptive changes in the neuronal mechanisms controlling sleep- and waking. Some of the notable mechanisms include:

- a) That chronic consumption of alcohol gradually desensitizes GABA receptor systems as well as decreases the production of GABA in the brain, which can lead to hyperactivity and an overstimulated nervous system. When an individual stops drinking alcohol, the sudden decrease in GABA production thus results in a range of withdrawal symptoms, including insomnia and disrupted sleep (Brower, 2001).
- b) That chronic consumption of alcohol also makes glutamate receptors hypersensitive to glutamate, thus

contributing to sleep disturbances and sleep fragmentation by arousal. Increased sensitivity of glutamate receptors and consequent activation of REM sleep-promoting neurons has also been proposed to contribute to the increased REM sleep pressure and abnormal phase advance in REM sleep (39).

- c) That chronic alcohol consumption causes a down-regulation of adenosine ENT1 expression, which is likely to contribute to sleep disturbances due to attenuated adenosinergic actions on wake-promoting systems.
- d) Alcohol can suppress melatonin production, a hormone that regulates the sleep-wake cycle (53). Thus a decline in melatonin levels likely contributes to difficulty falling and maintaining sleep.

4. Conclusions

In conclusion, alcohol consumption and sleep disturbances are closely linked. While alcohol may initially promote relaxation and sleep, excessive and chronic consumption can lead to disrupted sleep patterns, sleep apnea, and alcohol-induced insomnia. These sleep disturbances can have significant negative consequences on an individual's physical and mental health, including daytime fatigue, decreased mental concentration and memory, reduced immune function, and an increased risk of accidents or injuries. Additionally, chronic sleep disturbances is a risk factor for various psychiatric problems, including depression and anxiety. Therefore, it is crucial to be mindful of alcohol consumption and to seek help if one is experiencing sleep disturbances or other negative consequences associated with chronic alcohol consumption.

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