Mechanisms underlying sleep-wake disturbances in alcoholism: focus on the cholinergic pedunculopontine tegmentum

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Abstract

Sleep-wake (S-W) disturbances are frequently associated with alcohol use disorders (AUD), occurring during periods of active drinking, withdrawal, and abstinence. These S-W disturbances can persist after months or even years of abstinence, suggesting that chronic alcohol consumption may have enduring negative effects on both homeostatic and circadian sleep processes. It is now generally accepted that S-W disturbances in alcohol-dependent individuals are a significant cause of relapse in drinking. Although significant progress has been made in identifying the socio-economic burden and health risks of alcohol addiction, the underlying neurobiological mechanisms that lead to S-W disorders in AUD are poorly understood. Marked progress has been made in understanding the basic neurobiological mechanisms of how different sleep stages are normally regulated. This review article in seeking to explain the neurobiological mechanisms underlying S-W disturbances associated with AUD, describes an evidence-based, easily testable, novel hypothesis that chronic alcohol consumption induces neuroadaptive changes in the cholinergic cell compartment of the pedunculopontine tegmentum (CCC-PPT). These changes include increases in *N*-methyl-D-aspartate (NMDA) and kainate receptor sensitivity and a decrease in gamma-aminobutyric acid ($GABA_B$) - receptor sensitivity in the CCC-PPT. Together these changes are the primary pathophysiological mechanisms that underlie S-W disturbances in AUD. This review is targeted for both basic neuroscientists in alcohol addiction research and clinicians who are in search of new and more effective therapeutic interventions to treat and/or eliminate sleep disorders associated with AUD.

Keywords

Alcohol addiction; glutamate; GABA; pedunculopontine tegmentum; receptor; sleep-wakefulness

1. Introduction

Moderate to severe alcohol use disorders (AUD) are chronic relapsing conditions that are progressive and have serious detrimental health outcomes. The development of AUD is characterized by frequent episodes of intoxication, preoccupation with alcohol, use of

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Area tegmentale → è un gruppo di neuroni localizzato in vicinanza della linea mediana sul pavimento del mesencefalo

Colinergica → fibre colinergiche, fibre del sistema nervoso autonomo, la cui azione è mediata dall'acetilcolina

Peduncolo pontino → Il NUCLEO PEDUNCOLO PONTINO (nuclei colinergici) insieme al locus coeruleus coinvolto nella regolazione della motilità viscerale. Attraverso tutte queste connessioni, questo nucleo coinvolto nelle funzioni motorie stereotipate, come la gestualità che si ha durante la locomozione. È coinvolto anche nel controllo dello stato di veglia

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alcohol despite adverse consequences, compulsion to seek and consume alcohol, loss of control in limiting alcohol intake, and emergence of a negative emotional state in the absence of the drug [1]. Excessive alcohol use is a major contributor to the burden of disease and a host of injuries (related to vehicular, industrial, and many other accidents) in the United States and many other developed and developing countries. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), more than 18 million people in the United States either abuse or are dependent on alcohol [2], with an annual cost to of approximately $235 billion, out of which more than $23.5 billion could be attributed to insomnia and other sleep disorders. Thus, the consequences of sleep problems in alcoholics are economically and clinically significant. AUD is now considered a neurobiological illness in which chronic high dose alcohol consumption leads to alcohol-induced neuroplastic changes in the normal neuronal circuitry involved in the regulation of adaptive behaviors(most notably reward related behaviors). During the last 50 years, a vast amount of clinical literature, as well as both basic human and animal research, have shown that alcohol has a profound impact on sleep and circadian rhythm [3–6]. Although significant progress has been made toward understanding the neurobiology of alcoholism [7–11] and the neurobiology of sleep [12–14], the neurobiological underpinnings that underlie the sleep-wake (S-W) disturbances associated with alcohol abuse and alcohol withdrawal have not yet been clearly identified.

Tre parti principali:
1) Stadi del sonno;
2) Riassunto degli effetti dell'alcool nel ritmo sonno-veglia;
3) Possibili meccanismi neurobiologici;

This review first describes the S-W stages in both human and other laboratory animals that are used to understand the mechanisms and functions of sleep. It then briefly summarizes alcohol's effects on S-W activity of non-alcoholics and alcoholics during active drinking and during withdrawal. Finally, based on the existing literature concerning the neurobiological mechanisms of sleep regulation and alcohol's effects on our brain, it describes possible neurobiological mechanisms underlying S-W disturbances in alcoholism.

2. Sleep stages in human and other mammals

Sleep in mammals is not a homogenous behavioral state, but rather is a continuum of mixed states that differ in their physiology, chemistry, and phenomenological experiences [12, 13]. Because some human sleep stages are named differently from those in animals, and since the present description on the possible neurobiological mechanisms of AUD is based on animal research, the following text describes the similarities and differences between human sleep stages and those of animals.

Human Non-Rapid Eye Movement (NREM) and Rapid Eye Movement (REM) sleep alternate throughout each of the four to six sleep cycles that occur every night. The most common and preferred animal models used in sleep research include the mouse, rat, and cat; in these animals, NREM-REM sleep cycles are much shorter than in human and non-human primates [12]. This cyclic NREM-REM sleeps epochs in rodents and cats continue throughout the day and night, except when the animal is engaged in activities that require wakefulness. In humans, NREM sleep is further subdivided into four stages (I, II, III and IV), each corresponding to an increasing depth of sleep [12, 13]. NREM Stage one (NREM-I) sleep is characterized by relatively low-amplitude (<50 µV) theta frequency activity (4–7 cycles per second (Hz) and vertex sharp waves in the EEG. Stage two (NREM-II) sleep is

characterized by the appearance of distinctive sleep spindles (lasting between 0.5–1.0 sec and peak amplitudes of 100 μV) composed of augmenting and decrementing waves at a frequency of 12–14 Hz and K-complex (a negative sharp wave followed immediately by a slower positive component) waveforms in the EEG. Stage three (NREM-III) sleep is characterized by the addition of high-amplitude (>100 μV) slow waves (1–4 Hz), with no more than 50% of the EEG record occupied by the slow waves. In stage four (NREM-IV), the EEG record is dominated by high-amplitude (150–250 μV) slow waves (1–4 Hz). Throughout this process, as the EEG frequency is decreasing and the amplitude is increasing, muscle tone progressively declines and may be lost altogether in most of the somatic musculature. Slow rolling eye movements first replace rapid saccadic eye movements of waking and then subside, with the eyes finally assuming a divergent upward gaze. The deepest stages of NREM sleep, III and IV, are collectively called slow wave sleep (SWS; also known as delta sleep). Distinctions between stages of NREM sleep in animal models differ slightly from those in humans. In the aforementioned animals, NREM sleep is normally subdivided into two stages (SWS-I and SWS-II). SWS-I is identified by the presence of sleep spindles in the cortical EEG. SWS-II is considered deep sleep and is identified by the presence of high-amplitude, low frequency waves in the cortical EEG (delta sleep). Human NREM stages I and II sleep are comparable to mouse, rat, and cat SWS-I, whereas stages III and IV NREM sleep in humans are comparable to the animal SWS-II [12, 13].

After varying amounts of time (depending upon the size of the animal and its brain), this progressive set of changes in the EEG reverses itself and the EEG eventually resumes the low-amplitude, fast character previously seen in waking [12]. Instead of waking, however, behavioral sleep persists. Muscle tone, which was first passively decreased during NREM sleep, is now actively inhibited. Stereotyped bursts of saccadic eye movements, called rapid eye movements (REMs), appear in the electrooculogram (EOG) and give this state the name REM sleep [12]. This phase of sleep has also been called activated sleep (due to increased EEG activation) and paradoxical sleep (to signal the maintenance of increased behavioral arousal threshold in the presence of the activated brain). Supplemental to these polysomnographic signs, other REM sleep-specific physiological signs are: myoclonic twitches in the facial, digital, and even major proximal skeletal muscles, pronounced fluctuations in cardio-respiratory rhythms, and core body temperature and penile erection in males and clitoral engorgement in females. Physiological signs of REM sleep in humans are, for the most part, comparable to physiological signs of REM sleep in the rat and cat. However, another sleep stage, one between SWS-II and REM sleep, has been identified mainly in rats and cats and is called the transitional sleep stage (tS-R) [12, 15]. During this transitional stage, the appearance of cortical EEG signs is similar to the cortical EEG of SWS-I and hippocampal and pontine EEG signs are similar in appearance to those during REM sleep, but with less intensity. Since most animal sleep studies have not recorded hippocampal and/or pontine EEG, such studies have often considered this stage to be SWS-I. Similarly, in sleep studies of healthy humans, hippocampal and/or pontine EEG cannot be recorded to help identify sleep stages. Therefore, based on EEG signs in humans, this transitional sleep stage has always been identified as Stage II NREM sleep [15].

‼️ 3. Effects of alcohol consumption on sleep-wake disturbances in non-alcoholics

In healthy non-alcoholics, acute consumption of alcohol 1–3 hours before bedtime decreases sleep latency, increases NREM sleep stages III & IV (also known as SWS), increases EEG power density in the delta frequencies (0.3 to 4 Hz), and decreases REM sleep during the first half of nocturnal sleep time [5, 6, 10, 16–23]. However, during the second half of nocturnal sleep time, wakefulness (W) and REM sleep increase resulting in severe disturbances in sleep architecture. Unlike alcohol consumption closer to bedtime, consumption of alcohol in the late afternoon (6 hours before scheduled bedtime) decreases sleep efficiency (i.e. continuous sleep), total sleep time, and REM sleep [24]. Consistent with human studies, animal studies performed in rodents have shown that acute treatment of alcohol reduces time of sleep onset (latency to sleep), increases SWS, and decreases REM sleep for about 3–6 hours, after which there are increases in W and rebound REM sleep [25–30].

‼️ 4. Effects of alcohol on sleep-wake disturbances in AUD

Several studies have investigated the effects of continued alcohol consumption in AUD individuals [3, 5, 6, 31–33]. These studies have shown that alcohol consumption in AUD individuals: increases sleep latency; decreases total sleep time; increases NREM sleep (which then returns to baseline levels during withdrawal); and suppresses REM sleep (which then either rebounds or returns to baseline levels during withdrawal). Additionally, on withdrawal nights, sleep latency increases and total sleep decreases, suggesting that alcoholic patients develop tolerance to the sleep-inducing effects of alcohol [20, 34]. Studies have also shown that chronic alcohol consumption increases daytime sleepiness and reduces daytime alertness, indicating that chronic alcohol use not only decreases total amounts of sleep but also alters normal circadian patterns of sleep pressure [35]. It has also been indicated that AUD individuals are susceptible to virtually every type of sleep problem [4, 6]. As in human studies, animal studies have shown that 6 weeks of chronic exposure to alcohol in water or in a liquid diet increases W and reduces both SWS and REM sleep during the light period, but decreases W and increases SWS during the dark period [36, 37]. Animal studies have also shown that continued alcohol consumption causes alterations in the circadian distribution of S-W stages [29, 36–38].

‼️ 5. Effects of alcohol withdrawal on sleep-wake disturbances in AUD

The most severe consequences of alcohol withdrawal appear during the initial week of abstinence, but protracted withdrawal symptoms may persist as long as 2 years [22, 39–48]. During alcohol withdrawal, sleep efficiency continues to be reduced. Also, there are increases in sleep latency, W, and REM sleep, and a decrease in NREM sleep [3, 43, 48–54]. Hallucinations of delirium tremens, a severe manifestation of alcohol withdrawal, represent an intrusion of REM sleep processes into the waking state [55], which is another indication of increased REM sleep pressure during alcohol withdrawal. In addition, alcohol withdrawal can also intensify other sleep disorders such as sleep apnea and periodic limb movements [49, 50, 56, 57]. In healthy people, the majority of REM sleep occurs during the

last third of the night, but in alcoholics that have been abstinent for 10 to 30 days, the majority of REM sleep occurs during the first two-thirds of the night, suggesting an abnormal phase advance in REM sleep [46]. Thus, early stages of withdrawal also produce alterations in the circadian pattern of REM sleep, which will often persist even during prolonged recovery from drinking [3, 43, 48, 49, 57]. Disrupted sleep patterns, especially both increased REM sleep pressure during early abstinence and continued insomnia, are predictive of relapse into drinking behavior [40, 43, 51, 53, 58–60]. There is evidence that some AUD individuals may resume drinking in an attempt to self-medicate their sleep problems [3]. Similar to human studies, animal studies performed in rodents suggest that insomnia-like symptoms, which include increases in W and REM sleep and reductions in total sleep time and delta activity, are observed during withdrawal in alcohol-dependent rats [29, 36, 37, 61–65].

6. Alterations in EEG activity in healthy adults and adults with AUD

For the quantification of baseline EEG activity changes, brain waves are typically divided into the following frequency bands: delta (0.1–3.5 Hz), theta (3.5–8 Hz), alpha (8–12 Hz), sigma (12–16 Hz), beta (16–32 Hz), and gamma (32–80 Hz). Some of these wave bands are again further divided arbitrarily as "fast" and "slow" (e.g. slow alpha: 8–10 Hz; fast alpha: 10–12 Hz; slow beta: 16–20 Hz; fast beta: 20–32 Hz). A number of studies have shown that the decreases in the predominant baseline frequency and increases in power spectrum are the most common effects of ethanol ingestion on the baseline EEG activity in healthy adults [66–72]. Low doses of alcohol ingestion, which cause behavioral arousal and euphoria, decrease mean amplitude of EEG and increase theta and alpha band activity [68, 70, 72, 73]. Higher doses of ingested alcohol produce depression of activity; decrease frequency and increase mean voltage in all frequency bands [74, 75]. Reports of ethanol-induced changes in beta activity are somewhat contradictory. For example, some have reported decreased beta power with subsequent replacement by alpha activity [67, 73, 76], increased beta activity [68, 76], both increases and decreases in mean frequency in the beta range [77], and no ethanol-induced effects on beta [78–80]. The baseline EEG activity pattern, even without ingestion of alcohol, can also be used as a physiological marker for the identification of individuals with predisposition of later alcoholism. A comparison of the baseline EEG activity of light and moderate drinkers who were negative for a family history of alcoholism showed that moderate drinkers exhibited greater spectral power and higher peak frequency in the beta band [73, 81]. EEGs in men with a positive family history of alcoholism show more fast alpha frequency activity than matched controls with negative family history [81, 82]. It is also shown that alcohol consumption elicited different EEG patterns, with greater increases in slow alpha activity, in men at high risk for development of alcoholism [81, 82]. High-intake binge drinkers exhibit higher spectral power than the non- and low-intake binge drinkers in the delta and fast beta (20–32 Hz) bands [83]. As in human subjects, ethanol-preferring (i.e. P strain) rats exhibit greater delta frequency activity and lower-peak theta frequency than the ethanol non-preferring (NP) line of rats [84, 85]. High-alcohol drinking (HAD) rats also exhibit greater spectral power for the delta and theta bands and higher activity in the fast beta (13–32 Hz) and fast alpha (9–12 Hz) bands compared to low-alcohol drinking (LAD) rats [86]. Alterations in resting EEG activity have also been described in the

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alcoholic patients [87–93]. Adults with AUD manifest less prevalent and lower alpha power and more prevalent and higher beta power than do those without AUD [89, 91, 94, 95]. It has also been shown that individuals with AUD exhibit higher theta power and lower delta power than do matched non-AUD controls [96–98]. In summary, the majority of baseline EEG activity investigations demonstrated that the mean power of EEG activity decreases in delta and alpha bands and increases in beta band in both individuals with AUD and in young adults at risk for the future development of AUD.

Some studies have also examined the acute effects of ethanol ingestion on the EEG gamma band activity rhythm. One EEG activity recording study in healthy social drinkers has reported that ingestion of 0.5 and 0.75 g/kg doses of alcohol suppressed auditory transient evoked gamma band (40-Hz) oscillatory response [99]. Another study, using magnetoencephalography (MEG) has shown that ingestion of 0.8 g/kg dose of alcohol increased peak amplitude and decreased peak frequency of visual grating and finger abduction paradigms-induced gamma band EEG activity [100]. Interestingly, it has also been reported that the early evoked gamma band response in the frontal and parietal regions during target stimulus processing is significantly less in male adolescent subjects, with a high risk for alcoholism, compared to normal control subjects [101]. This finding suggests that the deficient early-evoked gamma band response may precede the development of AUD and could be a potential endophenotypic marker of AUD risk. High density EEG activity recording studies have shown that with either compared with non-AUD subjects or light drinkers, heavy drinkers and drinkers with more severe AUD exhibit increased synchronization in the gamma band, a sign of an abnormal changes in hippocampal-neocortical connectivity in heavy drinkers and a sign of a premature form of ageing in those with more severe AUD [102–104]. In summary, the mean powers of EEG activity decreases in delta and alpha bands and increases in beta and gamma bands in heavy drinkers, young adults predisposed with the future development of alcoholism, and AUD.

The findings described above regarding changes in EEG activity associated with the chronic excessive alcohol consumption of alcohol may provide a basis for identification of novel interventions for the treatment of AUD. They suggest to us that drugs that can produce a shift in the EEG activity pattern by decreasing high-frequency beta band and increasing low-frequency alpha band, perhaps, also increase evoked gamma band activity may be good candidate medications for testing in future AUD treatment clinical investigations. Consideration should also be given to the possibility that drugs that have specific effects on EEG activity, such as increasing alpha-band activity can be targeted to treat AUD individuals who display a particular EEG pattern such as decreased alpha activity.

7. Use of animal models to study alcoholism

One of the challenges in designing pre-clinical studies of the effects of ethanol consumption on sleep is the selection of the appropriate animal model of chronic alcohol exposure. A major problem that investigators confront is that outbred strains of rats will not, under normal circumstances, voluntarily consume alcohol in sufficient amounts to produce levels of intoxication that can be considered to be equivalent to those seen in humans with alcohol use disorders and which produce reliable states of alcohol dependence. To address this

Descrizione dei metodi utilizzati per esporre i ratti all'alcol

problem several models of chronic alcohol exposure have been developed in rodents (i.e. rats and mice) that lead to sustained blood alcohol concentrations that are in the range of those observed in individuals with AUD. Models used in sleep studies, thus far, include the delivery of alcohol using intragastric intubation, as a vapor, or via ethanol-containing liquid diets.

The administration of alcohol by intragastric administration has been used successfully in several studies to examine the effects of alcohol administration on S-W activity in the rat [29, 30, 38, 104–106]. The intragastric procedure can produce dependence in periods as short as 4 days [107]. High doses of ethanol, when administered intragastrically, can produce marked signs and symptoms of withdrawal including convulsive seizures [108, 109]. The use of the intragastric intubation for the delivery of alcohol has clearly been demonstrated to produce disruptions in S-W activity in the rat and mouse, which have similarities to alcohol-induced changes in this activity that are seen in individuals with alcohol use disorders [28, 38, 63, 104–106]. This procedure, however, lacks face validity as a model of alcoholism in that it involves the passive delivery of single large boluses of alcohol administered over a relatively short time interval, i.e. a few days. Of major concern is that very large doses of ethanol may produce toxic insults to the brain that may not occur in animals that self-regulate their intake of alcohol. Also, a single bolus of ethanol may not interact with the mechanisms that regulate sleep in a manner similar to that, which would be observed when ethanol intake fluctuates repeatedly throughout the day with intermittent ingestion of alcohol only during periods of wakefulness. A final concern is that the intragastric administration of alcohol using gastric intubation is in itself a highly stressful procedure that may produce behavioral and other effects that may not be seen when ethanol is administered under less stressful conditions.

Another method that has been employed by a few investigators in studies of the effects of ethanol on sleep is the use of a liquid diet as a vehicle for the delivery of alcohol [29, 36, 37]. The repeated ingestion of liquid diet containing 10% ethanol may lead to blood alcohol concentrations of more than 200 mg/dl [110]. The amount of ethanol consumed by animals given access to ethanol liquid can be large enough to produce signs of withdrawal after the discontinuation of access [110, 111]. Use of the ethanol liquid diets allows for the consumption of alcohol over extended periods of time, i.e. over many weeks, and animals self-regulate their intake of alcohol allowing this to occur with the daily fluctuations of S-W activity. Consequently, patterns of ethanol intake may have similarities to those seen in AUD. Animals, however, are essentially forced to consume alcohol and, consequently, the face validity of the liquid ethanol diet procedure as a model of human alcohol use disorders must be considered to be limited. In our ongoing studies of the neurobiological mechanisms underlying alcohol dependence in the rat model, ethanol is delivered in 9% concentration in a liquid diet. The results of this ongoing research showed that this experimental method was very effective in inducing a sleep phenotype of alcohol dependence and alcohol withdrawal (Fig. 1). A number of studies in the rat model have indicated that 9% ethanol in liquid diet delivers approximately 10 g/kg to 16 g/kg of ethanol per day with an average blood concentration in the range of 120 to 400 mg/dl [29, 111–113]. It has also been shown that a 9.0% (v/v) ethanol liquid diet produces sufficient dependence to enhance levels of responding for ethanol during periods of withdrawal [114]. Acoustic startle response, a

measure of excitability, remains elevated above control for at least 72 hours after discontinuation of a 8.7% liquid ethanol diet. Changes in daily distributions of SWS and REM sleep were seen in rats given a 6% liquid ethanol diet over periods of 3 to 6 weeks [29, 37].

Alcohol dependence can also be produced in animals by exposing them to ethanol vapors [115]. This procedure allows for the continuous delivery of ethanol in doses high enough to allow alcohol blood concentrations to reach the range of between 150–200 mg/dl. Delivery of ethanol in vapor form does not stress animals to which gastric intubation may and allows for ethanol to be administered on chronic basis. Several groups of investigators have used the ethanol vapor procedure to examine the effects of chronic ethanol exposure on sleep related EEG activity during withdrawal in rodents [61, 116, 117]. In mice exposed to ethanol changes in sleep architecture including reduced non-REM sleep and increased REM sleep corresponded to those seen in humans during withdrawal [116]. The limitations of the ethanol exposure procedure are that animals do not regulate their own intake of alcohol and that continuous exposure to alcohol vapors would not be expected to have fluctuations in blood alcohol concentration that are related to patterns of S-W activity. Another major limitation of this method is that it negatively affects the physiology of the respiratory system.

Several methods of chronic alcohol self-administration have been developed that have not yet been used to study the effects of alcohol on S-W activity. These include intra-gastric ethanol self-infusion [118], intermittent access to high dose ethanol [119], and ethanol self-administration by strains of alcohol-preferring rats [120]. All of these procedures can produce blood alcohol concentrations that are seen in individuals with AUD. They all offer the advantage of animals controlling their own intake of alcohol. As such they offer the opportunity to study the effects of alcohol on sleep using models of AUD with improved face validity in which alcohol concentrations vary in synchrony with animals' S-W cycles.

8. Possible mechanisms of alcohol's action in producing sleep-wake disturbances

Since the neurobiological mechanisms underlying alcohol's effects on S-W behavior remain poorly understood, our tentative explanation of these mechanisms will rely heavily on the well-known neurobiological mechanisms of S-W regulation and neurobiology of alcohol addiction. There are some excellent reviews on the basic neurobiology of S-W behavior and neurobiology of alcohol addiction [7–12, 14, 121].

8.1. In non-alcoholics

It is already known that γ-aminobutyric acid (GABA) and glutamate receptors are the major targets for ethanol, and, more specifically, that ethanol activates GABA receptors and inactivates several glutamate receptors including L-α-amino-3-hydroxy-5-methyl-isoxazole-4-proprionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors [122–127]. Ethanol also increases the activity of GABA receptors by facilitating the release of GABA and by elevating levels of neuroactive steroids that act to positively modulate

GABA$_A$ receptor systems [128, 129]. Also, both GABA and glutamate receptors are involved in the regulation of S-W states [12, 13, 81, 130–138], specifically: a) Increased release of GABA from the preoptic-hypothalamic areas (POA) activates GABA receptors (mainly GABA$_A$-type) on the neurons in the W-promoting areas of the brain that ultimately induce SWS (for details of this mechanism, see [12]); b) Activation of GABA$_B$ receptors on pedunculopontine tegmental (PPT) cholinergic cells suppresses neuronal activity, which in turn suppresses both REM sleep and W [135, 138]; c) Inhibition of NMDA-type glutamate receptors on PPT cholinergic cells suppresses W and inhibition of kainate-type receptors suppresses REM sleep [130–133]. Therefore, it is logical to suggest that the primary causal mechanisms of acute alcohol consumption-induced increased SWS could be the inhibition of W-promoting neurons via activation of GABA$_A$ receptors, whereas decreased REM sleep could be caused by the activation of GABA$_B$ receptors and/or inhibition of kainate-type of glutamate receptors on PPT cholinergic cells. It has been recently shown that ethanol treatment increases extracellular levels of adenosine [38], which is a metabolite known to participate in the GABA$_A$ receptor activation-mediated induction of SWS, via activation of neurons in the W-promoting areas of the brain [12]. Therefore, it is likely that the SWS-increasing effect of alcohol may be caused by both GABA$_A$ and adenosine receptor activation-mediated inhibition of cells in the W-promoting areas of the brain [12].

8.2 In actively drinking and abstinent alcohol-dependent individuals

A large number of studies on the neurobiology of alcoholism have provided evidence to show that chronic exposure to high alcohol doses during the transition from non-harmful alcohol use to AUD induces adaptive changes in neural circuits that control motivational processes, including arousal, reward, and stress [9, 123]. These neuroadaptations produce changes in sensitivity to alcohol's effects following repeated exposure (i.e., sensitization and tolerance) and during a withdrawal state following discontinuation of alcohol use [9, 123, 139, 140]. Alcohol interacts with many neurotransmitters and neuromodulators (e.g., dopamine, DA; serotonin, 5-HT; norepinephrine, NE; acetylcholine, Ach; GABA; glutamate; adenosine; opioid; orexin; ghrelin; corticotrophin-releasing factor, CRF; and neuropeptide Y) in the brain's reward and stress circuits to produce its positive and negative reinforcing effects. These interactions also can lead over time to neuroadaptations to alcohol-induced changes in neuronal function [9, 10, 122, 123, 140–152]. In alcoholism, neuroadaptation means that in response to chronic exposure to alcohol, the brain adjusts neuronal activity to compensate for alcohol's effects on neuronal functioning to maintain its "normal" activity levels. Major features of neuroadaptation to chronic alcohol consumption include decreased inhibitory response of GABA$_A$ receptor systems [153, 154] and hyperactivity of excitatory glutamate receptor (i.e. AMPA, NMDA, and kainate) systems [3, 5, 6, 9, 122, 123, 140, 142, 155]. There is also evidence of diminished responsiveness of pre-synaptic GABA$_B$ receptors to its agonist, baclofen, in the hippocampus during withdrawal from alcohol [156]. With chronic ethanol administration, tolerance may develop to ethanol-induced elevation of neuroactive steroids [157].

Ethanol-induced functional changes in AMPA, GABA$_A$, and NMDA receptor systems may be related, in part, to changes in the levels of expression of specific receptor subunits in select brain regions, including the amygdala, cerebral cortex, and hippocampus, which is of

importance because the subunit composition of these receptors determines their propensity towards either hyperexcitability or inhibition of excitability as well as their sensitivity to alcohol and other sedative agents [153, 158]. When alcohol is discontinued, these alterations may persist, at least for a while, resulting in increased arousal that manifests as withdrawal symptoms, including S-W disruptions.

Interestingly, one of the major brain areas in the S-W regulating network that actively regulates both W and REM sleep is the cholinergic cell compartment of the PPT (CCC-PPT) [12, 13, 136, 159]. For example, neuropharmacological and physiological studies have shown that glutamatergic activation of kainate receptors on PPT cholinergic cells induces REM sleep by raising neuronal activity to a medium level, whereas glutamatergic activation of NMDA receptors on these same PPT cholinergic cells induces W by increasing neuronal activity to its highest level [12, 130–133, 159, 160]. On the other hand, GABAergic activation of GABA$_B$ receptors inhibits these PPT cholinergic cells, which in turn suppresses both REM sleep and W and increases SWS [135, 138]. If the neuroadaptation theory is also applicable for the PPT (discussed above), then it is likely that the PPT of AUD individuals will exhibit reduced sensitivity to GABA$_B$ receptor activation, which could potentially increase W and REM sleep and decrease SWS [13, 135, 139]. Based on this neuroadaptation theory, it is also likely that the PPT of AUD individuals will have increased sensitivity of kainate and NMDA receptors. Again, this type of neurochemical condition in the PPT is ideal for increasing W and REM sleep and suppressing SWS [12, 130–133, 159, 160]. In support of this suggestion, one pharmacological study on human subjects has shown that decreased SWS and increased REM sleep pressure after alcohol withdrawal is caused by the increased sensitivity of cholinergic system [161]. Based on this evidence, we suggest that the CCC-PPT is one of the major targets of alcohol-associated neuroadaptation, which ultimately causes S-W disturbances, but this hypothesis has not yet been examined.

The suprachiasmatic nucleus (SCN) is critical in synchronizing circadian rhythms and these rhythms can be observed in outputs such as the patterning of the S-W cycle, core body temperature, and secretion of endogenous hormones [162–168]. Based on a vast amount of anatomical, physiological, pharmacological, and molecular evidence, it has been suggested that the PPT and basal forebrain (BF) cholinergic inputs to the SCN are crucial for maintaining normal circadian rhythm, and over-activation of these cholinergic systems could result in phase advance of circadian rhythms [162, 164, 169, 170]. In alcohol-dependent individuals, one of the major signs of S-W circadian disturbances is the abnormal phase advance in REM sleep. It is already known that the majority of BF cholinergic cells are involved in the induction of W while the other cells are involved in the induction of SWS, but both of these cell groups suppress REM sleep [12, 171, 172]. On the other hand, activation of PPT cholinergic cells increases REM sleep [136]. Therefore, in alcohol-dependent individuals, phase advance in REM sleep could potentially be caused by the over-activation of cholinergic cells in the PPT (but not in the BF).

As discussed above, research on alcohol and sleep has suggested that REM sleep pressure is predictive of relapse into alcohol drinking. Interestingly, research in drug addiction has demonstrated that the primary mechanism for relapse (i.e. reinstatement of drug-seeking behavior, an animal model of relapse) involves activation of glutamatergic cells in the

[margin note] cholinergic cell compartment of the pedunculopontine tegmentum

[margin note] Quindi aumentanno i momenti di wakeness e di fase REM → sonno più disturbato!

medial prefrontal cortex (mPFC), which then activates dopaminergic (DAergic) projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) [173–179]. Additionally, a number of anatomical, behavioral, physiological, and pharmacological studies have provided evidence to demonstrate that the CCC-PPT receives excitatory input from the mPFC [179–182] and sends cholinergic afferent projections to the VTA [183–186], where they synapse on DAergic neurons that then project to the NAc [180, 181, 187–195], resulting in the release of DA in the NAc [183, 196–198]. Furthermore, administration of a partial nicotinic receptor agonist varenicline has been shown in both preclinical and clinical trials to reduce ethanol consumption [199–202]. Given the role of the VTA in mediating the rewarding effects of ethanol and in reward prediction, it is plausible that the PPT, via its anatomical connection with this structure, may play an important role in the reinstatement of alcohol-seeking behavior, but this hypothesis has not yet been examined.

Orexin/hypocretin, NE, and CRF are also known to modulate W behavior [12] and they act in concert in the extended amygdala to modulate stress-related components of addiction [7–9, 148] and might be involved in the promotion of W in AUD S-W disorders, but this has not yet been supported by empirical evidence. Also, there is no evidence linking increased Orexin/hypocretin, NE, or CRF neurotransmitters to the enhancement of REM sleep amount or pressure. Another neurotransmitter, 5-HT, is also known to participate in the regulation of the S-W cycle [12]. There is a well-established link between 5-HT depletion, impulsivity, and alcohol-drinking behavior in rats and humans [146, 203–205]. During alcohol withdrawal, 5-HT release in the NAc of rats is suppressed, and this reduction is partially reversed by self-administration of alcohol during withdrawal [206]. It is also known that this decreased 5-HT activity favors cholinergic activation-mediated REM sleep induction [12]. Therefore, changes in the 5-HT system may also participate in the PPT cholinergic system-mediated S-W disturbances in abstinent alcoholics. However, some other studies have suggested that 5-HT may in fact not be involved in the S-W disturbances in AUD individuals [3, 5, 6].

Our working conceptual model is designed to illustrate only the possible mechanisms of S-W disturbances in alcohol addiction, focusing only on the role of the PPT in the development of sleep disorders that result from chronic exposure to ethanol (Fig. 2). Given the known anatomical connections between the PPT and the VTA, it seems reasonable that changes in PPT activity might influence drug relapse via this structure. This is clearly suggested by the finding that lesioning of the PPT blocks the expression of ethanol-induced reward, as measured by place preference, only in dependent withdrawn mice [207]. In addition to its role in mediating the rewarding effects of ethanol, the VTA is also implicated in mediating the prediction of the availability of rewards (via phasic firing of dopaminergic neurons) [208, 209] and signals for aversive stimuli [210]. Collectively, this evidence suggests that the PPT may act via the VTA to influence alcohol consumption and seeking behaviors. Thus, the neuroadaptation at the level of CCC-PPT may be critical patho-physiological mechanism for the S-W disturbances in AUD.

The hypothesis that S-W disturbances in AUD may be caused by the neuroadaptation at the level of CCC-PPT (hypersensitivity of kainite and NMDA receptors) is also supported by the findings that gamma band activity increases in AUD [102, 103]. For example, all cells in

the CCC-PPT are geared to fire at gamma band frequencies and the generation of this activity involves voltage-dependent high threshold N- and P/Q-type calcium channels [reviewed in 211–214]. It has been suggested that this CCC-PPT-mediated gamma band activity generation during REM sleep involves kainate receptor mediated activation of intracellular protein kinase A (PKA) and during wakefulness it involves NMDA receptor activation-mediated activation of intracellular CaMKII [reviewed in 211, 212]. Therefore, the increased gamma band activity in AUD is likely to be due to increased kainate and NMDA receptor sensitivity in the CCC-PPT.

9. Concerning remarks   Andare a vedere Figure 1 a pagina 23

The CCC-PPT plays a key role in regulating both W and REM sleep. Many of the receptor systems, including the NMDA, kainate, and $GABA_B$ systems whose activity is altered by the administration of ethanol have been implicated the regulation of W and REM sleep by the CCC-PPT. Given the evidence that chronic exposure to ethanol may enhance the excitability of NMDA and kainate systems, while, based on less extensive evidence, decreasing the sensitivity of $GABA_B$ receptors in several brain regions, it seems reasonable to hypothesize that similar alterations in CCC-PPT may play a role in the disruption in W and REM sleep that are seen with chronic alcohol use and during withdrawal from alcohol. This hypothesis can be tested by both examining molecular evidence of alcohol-induced changes in receptor subunit expression within the CCC-PPT and evaluating alterations in sensitivity to the effects of $GABA_B$ and excitatory glutamate receptor agonists on W and REM sleep that result from chronic exposure to ethanol.

Acknowledgments

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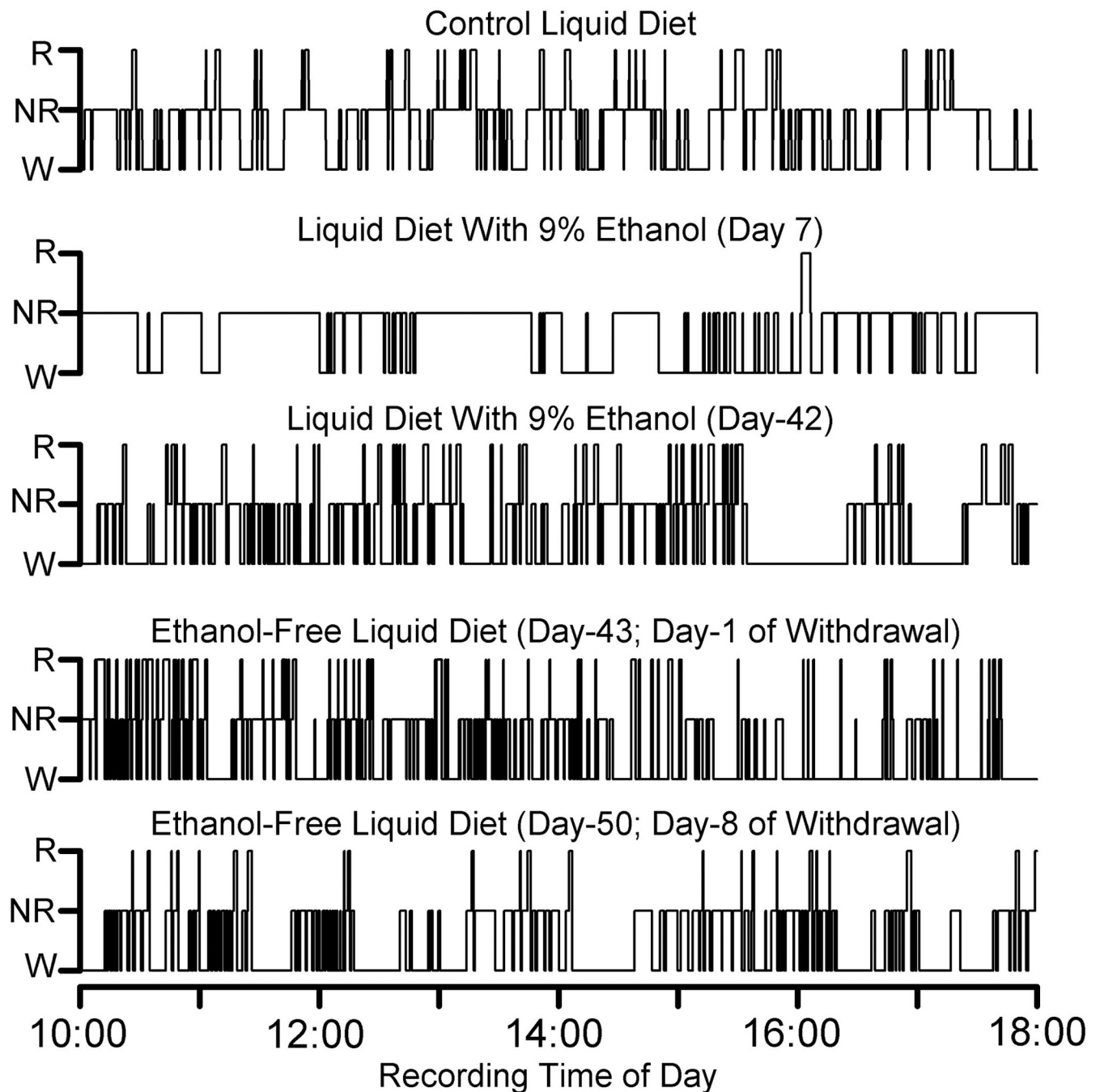
Control Liquid Diet

Liquid Diet With 9% Ethanol (Day 7)

Liquid Diet With 9% Ethanol (Day-42)

Ethanol-Free Liquid Diet (Day-43; Day-1 of Withdrawal)

Ethanol-Free Liquid Diet (Day-50; Day-8 of Withdrawal)

Recording Time of Day

Figure 1.
Typical example of the progression of sleep-wake architecture that occurs in rats over the course of 6 weeks of chronic alcohol consumption followed by 8 days of alcohol abstinence. The dose of ethanol in the liquid diet was increased gradually during the first 5 days: 3% ethanol on the first 2 days, 6% ethanol on the third and fourth days, then 9% ethanol (full dose) from the fifth day until the end of the 6-week period. Control animals received an ethanol-free liquid diet of equal caloric content (adjusted with dextrose). Then, from the beginning of the seventh week to the end of eighth week both groups of rats received an

ethanol-free liquid diet with a caloric content identical to that of the liquid diet consumed during the previous 6-week period. These continuous step hypnograms plot occurrence and duration of polygraphically and behaviorally defined wakefulness (W), non-REM sleep (NR; i.e. SWS), and REM sleep (R). Note that at the beginning of alcohol consumption, W and R decreased while NR increased. However, after a long period of continual alcohol consumption (6 weeks), W and R pressure increased while NR decreased. Then, during the initial period of withdrawal (Day-1), W and R pressure further increased while NR further decreased. Also, phase advance of R is clearly evident in both the final day of alcohol consumption and the first day of withdrawal. Finally, after 8 days of withdrawal, the S-W architecture of alcohol consuming rats began to resemble that of the control liquid diet-consuming animals.
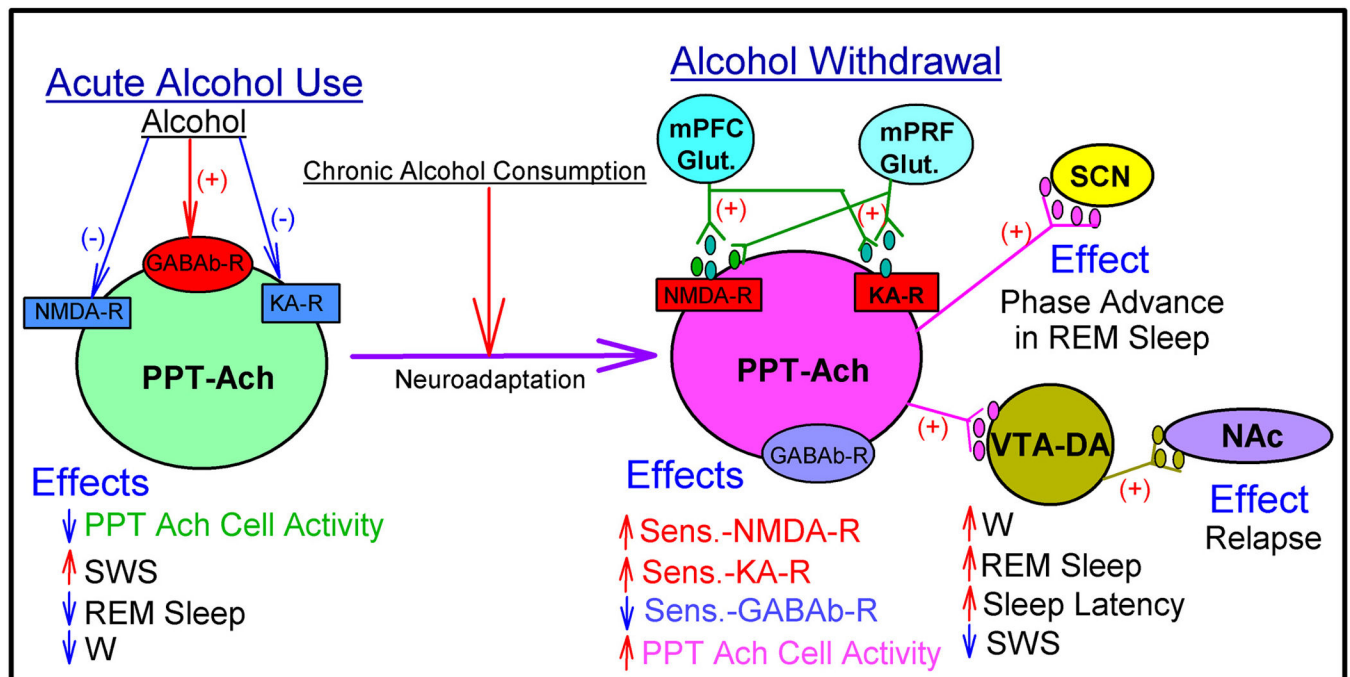
Figure 2.
A working model of the mechanisms underlying sleep-wake disturbances in chronic alcohol consumption. This model illustrates the neurobiological mechanisms underlying the effects of alcohol on sleep-wake disturbances. The text for this model is discussed above. Abbreviations: NMDA-R, NMDA receptor; GABAb-R, GABA-B receptor; KA-R, kainate receptor; PPT-Ach, pedunculo-pontine tegmental cholinergic cell; SWS, slow-wave sleep; REM sleep, rapid eye movement sleep; W, wakefulness; mPFC, medial prefrontal cortex; mPRF, medial pontine reticular formation; Glut., glutamatergic cells; SCN, suprachiasmatic nucleus; VTA-DA, ventral tegmental area dopaminergic cell; NAc, nucleus acumbens; Sens., sensitivity; (+), activation; (−), inhibition; ↑, increase; ↓, decrease.