Sleep Medicine Reviews 43 (2019) 92–95

Contents lists available at ScienceDirect

Sleep Medicine Reviews

journal homepage: www.elsevier.com/locate/smrv

CLINICAL REVIEW

The neurophysiological and neurochemical effects of alcohol on the brain are inconsistent with current evidence based models of sleepwalking

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ARTICLE INFO

Article history:
Received 31 July 2018
Received in revised form
6 September 2018
Accepted 24 October 2018
Available online 10 November 2018

Keywords:
Sleepwalking
Alcohol
Pathophysiology
Frontal motor cortex
Cingulate cortex GABAA
State dissociation
Inhibition

SUMMARY

The DSM-5 and ICSD-3 have removed alcohol from the list of potential triggers for sleepwalking due to the lack of empirical evidence. Recent imaging and EEG based studies of sleepwalking and confusional arousals have provided a more data-based method of examining if alcohol is compatible with what is known about the neurophysiology and neurochemistry of sleepwalking. These studies have demonstrated a deactivation of the frontal areas of the brain, while the cingulate or motor cortex remains active and characterized activation in the form of beta EEG. This increase in activation is attributed to a decrease in the inhibitory activity the neurotransmitter GABAA. This cerebral excitability of the cingulate cortex of sleepwalkers is also present in the brains of sleepwalkers during wakefulness compared to normal controls. Alcohol is well established to have an inhibitory effect on the brain and specifically on the motor areas via the inhibitory effects of increased GABAA activity. Thus, the empirical data show sleepwalking is characterized by a decrease in the inhibitory activity of GABAA – permitting or facilitating motor activity while alcohol has the opposite effect of increasing GABAA and inhibiting motor activity. This is inconsistent with theories that alcohol is somehow a trigger or facilitator for sleepwalking.

Introduction

Alcohol has appeared in some lists of potential triggers for sleepwalking for many years [1]. However, these lists have never provided any empirical proof of this relationship. This should not be surprising as there are no direct empirical studies of the effects of alcohol on sleepwalking. None the less, reference to alcohol as a sleepwalking trigger continues to occasionally appear in articles, reviews and book chapters and as part of sleepwalking defenses for otherwise criminal acts in alcohol intoxicated individuals. However, when a citation or reference is provided it is almost always to another review article or book chapter that in turn fails to provide a reference to any empirical proof, etc. etc. In this manner the "belief" that alcohol is somehow a trigger for sleepwalking is perpetuated. However, a belief is not proof. In the absence of any empirical evidence one would think that continued reference to alcohol as a trigger for sleepwalking would have ceased. Or perhaps this is exactly the reason this belief has persisted.

As a result of the influence of the Evidence Based Medicine (EBM) [2] movement, the leading classification systems have reevaluated the relationship between alcohol and sleepwalking and found it to be lacking a basis in reliable scientific evidence. The current editions of the International Classification of Sleep Disorders (ICSD-3) and the Diagnostic and Statistical Manual (DSM-5) have removed alcohol from the list of potential triggers for Disorders of Arousal such as sleepwalking, confusional arousal and sleep terrors [3,4]. The ICSD-3 states further that sleepwalking should not be diagnosed in the presence of alcohol intoxication. The DSM-5 warns that severe alcohol intoxication and alcohol blackout can be mistaken for sleepwalking or related disorders.

Advocates of the alcohol induced sleepwalking theory never point to the impressive body of scientific evidence of the effects of alcohol on brain and behavior. To date, there has been no

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https://doi.org/10.1016/j.smrv.2018.10.003
1087-0792/

examination of the extensive scientific literature on alcohol, brain and behavior to determine if the effects of alcohol are compatible with what is known about the neurophysiology and neurochemistry sleepwalking as there were no reliable published studies for comparison. However, a series of brain imaging and sophisticated EEG studies of sleepwalking – some during actual episodes of sleepwalking or confusional arousal – now make this examination possible.

Known pathophysiology of sleepwalking

Early theories of sleepwalking ranged from demonic possession to acting out of suppressed traumatic memories [5]. More recently, the concept of state dissociation – a mixing of wake and NREM sleep has gained general acceptance [6]. Sleep laboratory based empirical studies in recent years have turned this theory into an evidence based neurophysiological and neurochemical model of sleepwalking and related disorders. This data-based model has identified simultaneous deactivation of the frontal areas of the brain with a paradoxical activation of the cingulate or motor cortex as underlying source of sleepwalking behaviors [7–13].

Earlier studies utilizing measurement of brain metabolism have reported a global reduction of metabolism in slow wave sleep (SWS) compared to wakefulness [14]. This reduction in brain metabolism compared to wakefulness is most apparent at the cortical level in the prefrontal cortex, anterior cingulate cortex and precuneus [15,16]. In a study employing an EEG/fMRI technique in normal controls after 36 h of total sleep deprivation, the authors found both frontal areas and the cingulate cortex was less active during sleep scored as SWS (slow wave sleep or N3) [17].

Cingulate gyrus and motor cortex

The cingulate gyrus and motor cortex are reported to be involved in the origin of complex motor behaviors and under the inhibitory control of associative cortices [18,19].

Bassetti and colleagues were the first using a single photon (SPECT) device to demonstrate that brain perfusion during a sleepwalking episode does not show the same patterns as in the sleep of normal controls. In normal sleepers there was reduced brain perfusion in the frontal–parietal associative cortex and in motor areas. However, in their sleepwalking subject, the posterior cingulate cortex also showed activation, similar to the level noted during wakefulness [7] (see Fig. 1).

More recent studies have replicated and extended this finding in the brains of clinically diagnosed sleepwalkers noting both functional and possible structural abnormalities.

A high-density EEG (HD EEG) study of scalp and source power topography of 15 age and sex matched adult sleepwalkers and normal controls showed a local decrease in SWA (slow wave activity) in the cingulate and motor cortex [11]. This suggested increased excitability was found to overlap areas identified by Bassetti et al. in his SPECT study. Additionally, the frontal and parietal areas remained deactivated compared to normal controls.

Three stereo EEG studies captured a NREM parasomnia in real time. They were characterized by the simultaneous presence of sleep-like patterns over of the frontal cortex characterized by an increase in delta band EEG and wake-like patterns characterized by beta EEG over the motor and cingulate cortex [8–10]. Beta EEG is characteristic of the waking motor cortex activity [13,20–22] and was noted during sleep related behaviors.

An examination of the 4 s preceding the onset of sleepwalking was conducted for EEG in the beta range of 24–30 Hz in Brodmann areas 33 and 24 – pregenual and ventral cingulate cortex. An increase in beta frequency EEG in the 24–30 Hz range was noted prior to arousals. These researchers reported these finding suggest some underlying dysfunction in sleep/wake controls that is not limited to full blown episodes of sleep walking [13]. However, this finding was not compared with age and sex matched control normal sleepers.

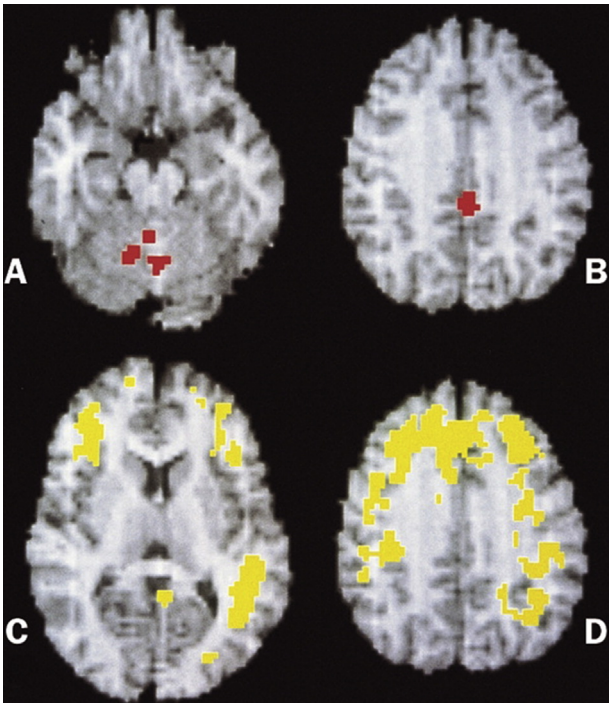

Fig. 1. Brain images of the 17-year-old patient during a sleepwalking episode as recorded in real time by single photon emission computed tomography. The highest increases of regional cerebral blood flow (>25%) during sleepwalking compared with quiet stage 3–4 non–rapid eye movement sleep are found in the anterior cerebellum (A) and in the posterior cingulate cortex (B). However, in relation to data from normal volunteers during wakefulness (n = 24), large areas of frontal and parietal association cortices remain deactivated during sleepwalking, as shown in the corresponding parametric maps. Note the inclusion of the dorsolateral prefrontal cortex (C), mesial frontal cortex (D), and left angular gyrus (C) within these areas.
From "SPECT During Sleepwalking," by C. Bassetti, S. Vella, F. Donati, P. Wielepp, and B. Weder, 2000, The Lancet, 356, p. 485. Copyright 2000 by Elsevier.

Functional changes in the brain of the sleepwalker during wakefulness

Additional studies have suggested that sleepwalking is not due just to some functional abnormality of the brain during sleep. Rather, the brains of sleepwalkers are also different from those of normal subjects while awake.

A study utilizing transcranial magnetic stimulation (TMS) tested the excitability of the motor cortex during wakefulness in a group of 8 clinically diagnosed sleepwalkers and a group of 12 age matched normal controls [22]. TMS is a well-established non-invasive method used to establish excitability of human cortex in many patient groups including epilepsy, multiple sclerosis, stroke, dystonia and Parkinsonism [23].

TMS testing showed that 3 standard measures of motor cortex functioning demonstrated increased excitability during wakefulness in sleepwalkers compared to normal controls [22]. The increased excitability of one of these measures was known to be strongly associated with impairment of GABAA transmission. GABAA is reported to be associated with the suppression of voluntary movements [24]. An additional measure of excitability is known to be related to impairment of cholinergic (ACH)

transmission. Thus, the authors suggest that increased excitability of the motor cortex due to dysfunction of GABAA and ACH explains sleepwalking due to 1) difficulty maintaining consolidated SWS, 2) inability to inhibit nocturnal movements and 3) reduced reactivity to sensory stimuli during episodes.

Structural abnormalities in the brain of sleepwalkers

A recent study has noted apparent structural changes in the posterior cingulate in a group of 14 sleepwalkers compared to 14 age and sex matched normal controls as measured by a 3 T MRI [12]. Statistically significant decreases in the volume of the left dorsal posterior cingulate cortex (area BA 23) and in the posterior midcingulate cortex (area BA24) were reported. This study remains to be replicated and the significance of this finding to sleepwalking to be explained.

The current research strongly supports the presence of functional and possibly structural abnormalities in the brains of sleepwalkers that are present during both sleep and wakefulness. There is general agreement that the frontal parietal areas are deactivated while simultaneously the cingulate gyrus and motor cortex remain at activity levels similar to or higher than that found during wakefulness. These changes in the motor cortex are related to a decrease in GABAA inhibition and suggest they may permit or facilitate motor activity during sleep in the sleepwalker.

Alcohol

The effects of alcohol on the brain and behavior have been extensively studied with thousands of empirical studies available for review.

Effects of alcohol on the neurophysiology and neurochemistry of the brain during wakefulness

Neurochemical

Alcohol is known to affect the brain via several neurochemicals. GABAA is one of the most widespread neurochemicals accounting for an estimated 25–50% of the CNS [25] It has been identified as the primary neurochemical affected by alcohol especially during acute alcohol intake [26]. Alcohol increases the inhibitory effects of GABAA and is reported to have a direct effect on the cingulate and motor cortexes resulting in deactivation.

Alcohol effects via GAGAA action have a significant effect on standing and posture. Alcohol may disrupt; 1. Nerve transmission at the synapse, 2. Impair vestibular function, 3. Decreases amplitude of reflexes, and increases the latency and decreases the height of long latency muscle responses [27].

Alcohol thus causes its inhibitory effects by increasing GABAA transmission and decreasing motor activity.

Effects of alcohol on the cingulate gyrus and motor cortex

Several studies have assessed the effects of alcohol on the motor cortex during wakefulness utilizing TMS and TMS/EEG techniques. A 1995 study utilized TMS in waking healthy volunteers before and after alcohol consumption [28]. All subjects were shown to have blood concentration of alcohol of 0.0 m/l before alcohol was administered. Thirty minutes after consuming 0.7 L of wine the blood alcohol level increased to between 0.6 and 1.0 ml/l. The main results of these studies were an increase in intracortical inhibition (ICI) and a decrease in intracortical facilitation related to the inhibitory effects of GABAA [28].

Another study employing a combined TMS/EED method was found to completely eliminate the N100 waveform typically evoked by the motor cortex. This was interpreted as the result of motor cortex inhibition and was attributed to the inhibitory effect of alcohol via GABA effects [29].

These TMS based data confirm that alcohol causes its effects on motor cortex by increasing inhibition via GABAA.

Discussion

The functional pathophysiology of sleepwalking based on recent imaging and EEG based studies is based on a paradoxically activated or reduced inhibition of the cingulate or motor cortex during sleep in addition to a deactivated frontal lobe [7–13,22]. The activated motor cortex is associated with a decrease in inhibitory GABAA activity that allows or even facilitates movements during sleep. These same motor areas in sleepwalkers during wakefulness remain more active than in normal controls. On the other hand, alcohol administered during wakefulness results in an increase in inhibitory GABAA activity and increased inhibition of the cingulate and motor cortex. This increased inhibition has been shown to inhibit a variety of motor cortex related actions.

Clonazepam, the drug of choice for treating Disorders of Arousal– also acts by increasing GABAA [30]. Other drugs with similar pharmacological profiles such as diazepam have also been reported to be effective treatments for sleepwalking [31].

Advocates of the alcohol-induced sleepwalking theory have focused on the absence of an empirical study of the effects of alcohol on sleepwalking, studies based on patient self-reports via questionnaires and the effects of alcohol on slow wave sleep (SWS) [5,6]. Alcohol has never been given to a clinically diagnosed sleepwalker and the effects measured during a sleep study. Studies referring to the retrospective self-reports of patients who believe that in the past alcohol has triggered episodes of sleepwalking fail to account for the fact that sleepwalkers have amnesia for past episodes. Additionally, this method requires those individuals to self-diagnosis those past episodes. The continued suggestion that alcohol increases deep sleep and that this primes the sleepwalker for episodes, lacks general and specific empirical support [7,8]. Recent reviews have found that in normal controls alcohol rarely results in a statistically significant increase in SWS as a % of total sleep time. When the sleep period is truncated – first 1/3, first ½, first 1–3 h, first 2–4 h etc. 6 studies reported a statistically significant increase in SWS. Finally, the definition of deep sleep or SWS (3) used by the American Academy of Sleep Medicine (N3) [9] or based on the Rechtshaffen and Kales Scoring Manual (S3+4) are arbitrary and difficult to apply consistently. A recent published study reported that interscorer reliability of the scoring of SWS – N3 – was extremely poor even between highly trained technologists [10]. Thus, current and past arguments that alcohol is somehow a trigger for sleepwalking lacks a basis in valid and reliable empirical research.

The neurophysiological and neurochemical data reviewed here is not the same as a direct empirical test of the effects of alcohol on sleep and sleepwalking in the sleep laboratory, with or without concurrent TMS, SEEG, SPECT or other sophisticated techniques. It is nevertheless directly related to functioning of the sleepwalker's brain and the underlying question of if and how alcohol is related to sleepwalking. Based on these studies, alcohol would be expected to interfere with or reverse one essential aspect of the pathophysiology of sleepwalking by increasing GAABA inhibition of the motor cortex. This hypothesis awaits direct empirical testing of the effects of alcohol during the sleep on normal subjects and clinically diagnosed sleepwalkers. The synthesis here of empirical data provides a basis in generally accepted sleep and alcohol neurophysiology and neurochemistry for ruling out a role for alcohol as a trigger for sleepwalking.

Practice points

1) Recent studies of the neurophysiology and neurochemistry of sleepwalking provide empirical support for removing alcohol as a trigger for sleepwalking
2) Functional and possible neuroanatomical differences in sleepwalkers are not limited to sleep but are present during wakefulness.

Research agenda

1) Direct empirical studies of the effects of alcohol during sleep on normal and sleepwalkers using combined polysomnography and imaging techniques need to be performed.

Conflict of interest

The author has no conflicts of interest.

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* The most important references are denoted by an asterisk.