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Original article

Caffeine challenge in insomniac patients after total sleep deprivation☆

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Abstract

Background and purpose: This study compared the effects of caffeine in patients with primary insomnia and normal volunteers. The main goal was to determine the differences in sensitivity to caffeine between the groups. We investigated the effects on daytime sleep of placebo or caffeine after a night of total sleep deprivation (SD). We hypothesized that insomniacs would be more affected by caffeine, which would suggest a change in adenosine receptor (number or sensitivity) in primary insomniacs.

Patients and methods: Six primary insomnia patients (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)) and six normal volunteers with no sleep complaints participated in a double-blind study with caffeine or placebo administered under a cross-over design with each subject serving as his or her own control. The participants did not have a history of drinking coffee or caffeinated beverages. Data from all-night polysomnography and multiple sleep latency test (MSLT) were collected in the sleep research laboratory of National Institute of Medical Sciences and Nutrition Salvador Zubirán.

Results: During the baseline night, patients with insomnia had significantly less delta sleep and less total sleep time than the normal volunteers. Mean sleep latency under basal MSLT did not differ between the groups. However, insomnia patients had significantly less total sleep during each nap compared to normal volunteers. After one night of total SD and under caffeine administration, the insomniacs had significantly longer sleep latency and less total sleep time in MSLT compared to normal volunteers. After SD, healthy volunteers reduced sleep latencies in MSLT with or without caffeine.

Conclusions: Patients with insomnia had a higher sensitivity to the diurnal awakening effect of caffeine even after one night of SD. This suggests that changes in the adenosine receptors could, in part, be responsible for the hyperarousal state that has been reported in primary insomnia.

Keywords: Insomnia; Caffeine; Sleep deprivation; Adenosine; Process 'S'; Multiple Sleep Latency Test

1. Introduction

Insomnia is defined as difficulty falling asleep, difficulty remaining asleep, early morning awakening and/or non-restorative sleep [1]. Insomnia is an important public health issue because it has a significant negative impact on an individual's physical and social performance, ability to work and quality of life [2,3].

The neuronal mechanisms underlying insomnia are still poorly understood. One possibility is that these individuals may have a low homeostatic drive for sleep that could be responsible for some sleep findings in insomnia patients [4]. For instance, after 21 h of sleep deprivation patients with insomnia had less slow wave delta activity compared to normal volunteers [4]. They also found that the mean duration of alpha rhythm was increased in insomnia patients.

Another possibility is that patients with insomnia are hyperaroused, which prevents them from falling asleep and

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maintaining sleep. This possibility is supported by a study comparing mood and personality of normal sleepers versus individuals with insomnia [5]. It was found that insomnia patients displayed increased tension/confusion, decreased vigor, personality disturbance, subjective overestimates of poor sleep, increased body temperature, increased 24-hour whole-body metabolic rate, and increased multiple sleep latency test (MSLT) values compared to normal sleepers. The authors concluded that some of the daytime symptoms were not related to the sleep deficiency but rather were due to hyperarousal of the central nervous system.

The hyperarousal theory is further supported by reports that some individuals with insomnia avoid taking caffeine or caffeine-containing beverages [6]. In one study involving only women, those with insomnia reported drinking less caffeine per day [3,6]. Caffeine is the most frequently used central nervous system (CNS) stimulant in the world. It is a methylxanthine that is rapidly absorbed when taken orally, with a distribution volume similar to that of total body water [7] and a half-life of approximately 3–8 h. The waking effect of caffeine is likely due to a non-selective blockade of adenosine receptors, particularly the A_1 and A_{2A} receptors [8]. Antagonism of the A_1 adenosine receptors on wake-active basal forebrain cholinergic neurons may prevent them from being silenced [9]. Similarly blockade of the adenosine A_{2A} receptors may prevent the sleep-active neurons in the preoptic area from becoming active [10,11].

The effects of caffeine on sleep architecture have been shown in normal volunteers [12]; caffeine is capable of antagonizing the cognitive impairment produced by prolonged sleep deprivation [11]. In rats, we determined that a reduction in sensitivity or number of adenosine receptors might contribute to the decline in sleep drive with aging [13]. Indeed, the elderly are told to avoid stimulating beverages such as coffee.

We hypothesized that a similar reduction in sensitivity or number of adenosine receptors might also contribute to low sleep drive and hyperarousal in some individuals with insomnia. To test this hypothesis, in the present study, the effects of caffeine were examined in patients with insomnia and normal volunteers.

2. Methods

Six patients with insomnia and six normal volunteers were studied. A written consent was obtained from all subjects after fully explaining the research procedure. All patients with insomnia met the diagnostic criteria for primary insomnia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and were discontinued from any pharmacological treatment for insomnia two weeks prior to the study. All subjects studied (i.e. patients as well as normal volunteers) were not regular consumers of caffeine, cola beverage or any other form of medicine with caffeine and did not have a history of regular coffee consumption (defined as more than five cups of coffee per week on a regular basis). All patients and normal volunteers were non-smokers and had never smoked.

The subjects were brought into the sleep laboratory and after a night of acclimatization a baseline polysomnography was obtained. The day after the nocturnal recording, the basal daytime MSLT was also obtained. All recordings were made on a Nicolet Ultrasom Workstation at an emulated paper speed of 10 mm/s and consisted of simultaneous monitoring of the electroencephalogram (EEG) (C3/A2, O2/A1), electrooculogram (EOG), surface mentalis and anterior tibialis electromyogram (EMG), and electrocardiogram (EKG) (Lead II). Quantitative evaluation of sleep stages was made visually with conventional Rechtschaffen and Kales [14] criteria with 30-second epochs for rapid eye movement (REM) and stages of non-rapid eye movement (NREM) sleep. The number of awakenings was scored as the number of times at least one 30-second epoch of wakefulness was scored after sleep onset. Respiratory movements were monitored using piezo-electric bands for thoracic and abdominal effort. Oral/nasal airflow was monitored by a four-bead thermistor system. Oxygen saturation (SaO_2) was recorded with an ear pulse oximeter BCI-9000. The number of abnormal breathing events per hour of sleep was quantified as the apnea and hypopnea index (AHI: apneas and hypopneas per hour of sleep). Apnea was defined as a decrease in respiratory airflow below 20% of the steady state amplitude preceding the breathing event. Hypopnea was defined as a reduction in respiratory airflow between 20% and 50% of the baseline with an oxygen desaturation of $>3\%$. The number of oxygen desaturations below 90, 80, and 65% per hour of sleep (SaO_2 80–90% index, SaO_2 65–79% index, and SaO_2 $<$ 65% index respectively); the cumulative oxygen desaturation (80–90%, 65–79%, and $<65\%$) in minutes (min) were also quantified. Apneas were considered central if there was a cessation of respiratory effort for at least 10 s, and obstructive if there was a cessation of oronasal airflow for at least 10 s, despite persistent respiratory effort. A patient was considered to have obstructive sleep apnea/hypopnea (OSAH) when the index (AHI) (number of apneas + hypopnea per hour of sleep) was >5.

Periodic limb movements (PLM) were scored according to Coleman's criteria [15]: a movement was scored when it occurred as part of a series of four consecutive movements that were separated by at least 4 but not more than 90 s, with a duration between 0.5 and 5 s. A patient was considered to have PLM (or nocturnal myoclonus) when the index (PLMI: number of periodic leg movements per hour of sleep) was >5. Before going to bed and after awakening all patients were asked if they had pain or indisposition. Recordings were scored by a certified sleep laboratory technician who was blind to the order of sleep procedures.

After the first and second night of polysomnography, a daytime MSLT was obtained. Subjects received four opportunities to sleep for 20 min in a private, darkened