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Original Article

The association between caffeine consumption and objective sleep variables is dependent on *ADORA2A* c.1083T>C genotypes

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ABSTRACT

Objective: To verify the association between c.1083T>C polymorphism in the adenosine receptor A_{2A} gene (*ADORA2A*) and objective sleep, as well as the correlation between caffeine consumption, sleep parameters, and electroencephalographic spectral power in a large, population-based sample from São Paulo, Brazil.
Methods: This study was conducted in participants of the São Paulo Epidemiologic Sleep Study (EPISONO), a large, population-based survey consisting of a representative sample of the inhabitants of the city from São Paulo, Brazil, according to sex, age (20–80 years), and socioeconomic status in the year 2007. Questionnaires, polysomnography, spectral analysis of sleep electroencephalogram, and c.1083T>C polymorphism genotyping were performed in this study.
Results: We found that caffeine consumption was positively correlated with sleep latency and α spectral power, as well as negatively correlated with percentage of N3 stage and δ spectral power in this stage. However, this association was identified only in T allele carriers and not in CC genotype.
Conclusion: Our data support an important aspect of this polymorphism in *ADORA2A* gene, showing that the variant affects the association between caffeine consumption and objective sleep parameters in a large population-based cohort.
Clinical trial information: Name: Epidemiology of sleep disturbances among adult population of the Sao Paulo City. URL: http://www.clinicaltrials.gov/ct2/show/NCT00596713?term = NCT00596713&rank = 1. Number: NCT00596713.

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1. Introduction

In our society, individuals have decreased their sleep duration in exchange for more hours at work, entertainment, or as a result of sleep disturbances, leading to a condition known as chronic sleep restriction. In this sense, the use of stimulants such as caffeine has become very common. Caffeine is a widely used methylxanthine due to its stimulating effects on the central nervous system (CNS). Low doses of caffeine have been already associated with positive subjective effects on mood. Griffiths et al. [1] demonstrated that 100 mg of caffeine increased alertness, well-being, social disposition, motivation for work, concentration, energy, and self-confidence compared to placebo, decreasing headaches and sleepiness [1]. A well-known mechanism by which caffeine promotes wakefulness is due to its antagonist effects of adenosine, an important endogenous neuromodulator associated with homeostatic sleep pressure and sleep promotion [2]. It has been previously found that adenosine accumulates after sleep deprivation, especially in the basal forebrain, and tends to return to baseline levels after sleep recovery, being considered an important sleep homeostatic factor [3]. Adenosine promotes sleep by binding to its receptors in the basal forebrain, mainly A_1 and A_{2A}, and caffeine exerts an antagonist effect, blocking this receptor and reversely canceling adenosine effects and promoting wakefulness [4].

Genetic variations in components of the adenosinergic system have been shown to be associated with alterations in sleep–wake cycle and electroencephalogram (EEG) patterns in healthy individuals, particularly in response to caffeine. Population-based studies have shown significant associations between a functional polymorphism in the adenosine deaminase gene (*ADA*) and

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alterations in sleep efficiency and slow-wave sleep [5], as well as with specific sleep EEG spectral power [6]. Regarding adenosine receptors, a previous study found that caffeine consumption was associated with reduction of sleep quality in self-rated caffeine-sensitive individuals, but not in caffeine-insensitive individuals [7]. Furthermore, the genotype distribution of the c.1083T>C polymorphism in the adenosine A_{2A} receptor gene (*ADORA2A*) differed between caffeine-sensitive and -insensitive individuals, and this polymorphism was able to predict how caffeine induction could change brain activities during sleep [8].

Taking into account the variety of studies about the role of the adenosinergic system on sleep homeostatic regulation, together with the evidence found by association studies, we hypothesized that genetic variations in this system could modulate sleep patterns in response to caffeine consumption. Thus, the aim of this study was to verify the association between c.1083T>C polymorphism in the adenosine receptor A_{2A} gene (*ADORA2A*) and sleep variables in a large, population-based sample from São Paulo, Brazil. In addition, we aimed to verify the effect of *ADORA2A* genotypes on the correlation among caffeine consumption, sleep variables, and EEG spectral power in this population.

2. Methods

2.1. Subjects

This study was conducted with participants of the São Paulo Epidemiologic Sleep Study (EPISONO), a large, population-based survey consisting of a representative sample of the inhabitants of the city from São Paulo, Brazil, according to sex, age (20–80 years), and socioeconomic status in the year 2007. A total of 1101 volunteers were filled out home-based questionnaires, and 1042 underwent in-laboratory polysomnography (PSG) recordings (refusal rate, five percent), specific questionnaire evaluation, and blood sample collection. Details of the EPISONO study were published by Santos-Silva et al. [9]. The study protocol was approved by the Research Ethics Committee of the Universidade Federal de São Paulo (CEP 0593/06) and was registered with ClinicalTrials.gov (number NCT00596713). All volunteers read and signed the informed consent form.

2.2. Caffeine consumption and caffeine load

To subjectively assess caffeine consumption, volunteers answered the following questions on the day of the PSG: (1) "On average, how many cups of coffee, black tea/tea, or soda-like drinks do you usually consume daily?" (2) "How many cups of coffee/black tea/tea or soda-like drinks have you consumed today?" (3) "If you consumed some of these drinks today, at what time of the day did you consume the last drink?" To evaluate the caffeine that individuals consumed on the day of PSG, taking into consideration both the number of cups and the time since the last cup, we proposed an index named "caffeine load," which consisted of the total number of cups taken on that day divided by the number of hours since the last caffeine-containing beverage was consumed.

2.3. Polysomnography

Full-night PSG was performed using EMBLA N7000 digital system (Embla Systems, Inc., Broomfield, CO, USA), respecting the usual hours of wake and sleep of each volunteer. The following physiological variables were monitored simultaneously and continuously: EEG (C3-A2, C4-A1, O1-A2, O2-A1), electrooculogram (EOG-Left-A2, EOG-Right-A1), electromyogram (EMG, submentonian region, masseter region, anterior tibialis, and seventh intercostal space), electrocardiogram (ECG, V1 modified derivation), airflow detection (thermocouple and nasal pressure), respiratory effort (thorax and abdomen) via x-trace belts, snoring, body position, and arterial oxygen saturation. Sleep stages were visually scored according to standardized criteria for investigating sleep [10]. To make it consistent with updated sleep stage nomenclature, we represented the results here as N1 (Stage 1), N2 (Stage 2) N3 (Stages 3 + 4), and REM sleep stages. Arousals, sleep-related respiratory events, and leg movements were scored in accordance with the criteria established by the American Academy of Sleep Medicine [11].

Obstructive sleep apnea syndrome (OSAS) was considered positive [12]. In individuals who presented with an apnea–hypopnea index (AHI) between five and 14.9, in addition to at least one of the following complaints: loud snoring, daytime sleepiness, fatigue, and breathing interruptions during sleep. Subjects with an AHI $\geq$15 were also considered positive for OSAS, regardless of whether they had any subjective complaint. Objective insomnia was defined as described previously [13]: individuals without regular insomnia symptoms were considered good sleepers. Individuals reporting regular insomnia symptoms (difficulties initiating or maintaining sleep, and/or early morning awakenings, occurring at least three times per week) that had little or no effect on daytime activities were classified as having insomnia symptoms. Individuals reporting frequent and persistent insomnia symptoms (lasting more than one month) that interfered substantially with daily functioning were categorized as having DSM-IV insomnia [14]. Individuals were evaluated for restless legs syndrome (RLS) based on standard criteria [15,16].

2.4. Spectral analysis of sleep EEG

Spectral analysis of sleep EEG was performed according to previous published studies [6,17]. In summary, EEG waves from C3-A2, C4-A1, O1-A2, and O2-A1 derivations were decomposed into δ (<4.0 Hz), θ (4.0–7.9 Hz), α 1 (8.0–9.9 Hz), α 2 (10.0–12.9 Hz), β 1 (13.0–17.9 Hz), β 2 (18.0–29.9 Hz), and γ (≥30.0 Hz) frequency bands using fast Fourier transformation (sampling rate of 200 Hz, 30-s epoch, low-frequency filter of 0.3 Hz; high-frequency filter of 35 Hz; time constant of 0.3 s, and notch filter of 60 Hz). Epochs consisting of the five percent with the highest signal amplitude (maximum–minimum) at each sleep stage were considered artifacts and excluded from analysis.

2.5. c.1083T>C polymorphism genotyping

Genomic DNA was obtained from peripheral blood leukocytes collected using ethylenediaminetetraacetic acid (EDTA)–containing tubes, using a modified salting-out protocol [18]. Genotyping of the c.1083T>C polymorphism in the adenosine A_{2A} receptor gene (*ADORA2A*) (rs5751876) was performed using an allele-specific polymerase chain reaction (PCR) assay protocol, the methodology of which has been previously described, with some modifications [7]. We used allele-specific primers designed for selective amplification of each allele and a universal reverse primer: A2A-F_T (forward primer specific for allele T: 5′-CGGAGGCCCAATGGCTAT-3′), A2A-F_C (forward primer specific for allele C: 5′-CGGAGGCC-CAATGGCTAC-3′) and A2A-R (reverse primer: 5′-GTGACTGGT-CAAGCCAACCA-3′). A positive control primer pair was used to amplify a region of the *HLA-DRB1* gene (forward primer: 5′-TGCCAAGTGGAGCACCCAA-3′; reverse primer: 5′-GCATCTTGCTCT GTGCAGAT-3′) to guarantee the correct functioning of the reaction. The PCR was performed in volumes of 15 μL containing 6 μL H_2O UltraPure DNase/RNase-Free Distilled Water (Life Technologies, USA), 7.5 μL *GoTaq* Green Master Mix (Promega, Madison, WI, USA), 0.3 μL A2A-F_T primer (for T allele reaction) at 10 μM or 0.3 μL A2A-

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