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Effect of caffeine on cervical vestibular-evoked myogenic potential in healthy individuals☆

Ana Maria Almeida de Sousa[a,*], Fabio Akira Suzuki[a,b]

[a] *Instituto de Assistência Médica ao Servidor Público Estadual (IAMSPE), São Paulo, SP, Brazil*
[b] *Universidade Federal de São Paulo (UNIFESP/EPM), São Paulo, SP, Brazil*

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KEYWORDS
Vestibular evoked myogenic potentials;
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Abstract
Introduction: Caffeine is the most common psychoactive drug in use around the world and is found at different concentrations in a variety of common food items. Clinically, a strong association between caffeine consumption and diseases of the vestibular system has been established. Cervical vestibular-evoked myogenic potential (cVEMP) is an electrophysiological test that is used to assess the sacculocollic pathway by measuring changes in the vestialibulocollic reflex.
Aim: The present study aimed to evaluate the effect of an acute dose of caffeine on the vestibulocollic reflex by using cVEMP.
Method: A prospective experimental study was performed in which healthy volunteers were submitted to the test before and after the intake of 420 mg of caffeine. The following parameters were compared: p13 and n23 latencies and p13-n23 amplitude.
Result: No statistically significant difference was found in the test results before and after caffeine use.
Conclusion: The vestibulocollic reflex is not altered by caffeine intake.

PALAVRAS-CHAVE
Potenciais evocados miogênicos vestibulares;
Cafeína;
Vertigem;
Tontura

O efeito da cafeína no potencial evocado miogênico vestibular cervical em indivíduos saudáveis

Resumo
Introdução: A cafeína é a droga psicoativa mais consumida no mundo e está contida, em diferentes concentrações, em diversos alimentos consumidos no dia a dia. Clinicamente, nota-se um envolvimento importante do seu consumo com as doenças do sistema vestibular. O VEMP cervical é um exame eletrofisiológico que avalia a via sáculo-cólica, determinando alterações no reflexo vestíbulo-cólico.
Objetivo: O objetivo deste trabalho é avaliar a interferência do uso agudo de cafeína no reflexo vestíbulo-cólico através do cVEMP.
Método: Foi realizado um estudo experimental prospectivo, no qual voluntários saudáveis se

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* Corresponding author.
E-mail: anamasousa@yahoo.com.br (A.M.A. Sousa).

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submeteram ao exame antes e depois do uso de 420 mg de cafeína, sendo comparados os seguintes parâmetros: latência de p13 e de n23 e interamplitude p13-n23.
Resultado: Após a comparação dos dados não houve diferença estatisticamente significante entre os exames antes e após o uso da droga.
Conclusão: Não foi observada influência da cafeína no reflexo vestíbulo-cólico.

Introduction

Caffeine is the psychoactive drug most widely consumed worldwide.[1,2] Like theophylline and theobromine, it is an alkaloid from the group called methylxanthines, differing from these substances by the presence of a third methyl group, identified as 1,3,7-trimethylxanthine.[3] At different concentrations, caffeine is present in several substances consumed in daily life: coffee, green tea, chocolate, cola drinks, guarana, yerba mate, among others (Table 1).[4,5]

Table 1 Main types of foods and beverages containing caffeine.

Item (milliliters – mL)	Caffeine content (milligrams - mg)
Tea (227 mL)	
Weak	25
Medium	42
Strong	51
Coffee (227 mL)	
Instant	45
Brewed	111
Cola drinks (330 mL)	35
Energetic drinks (240 mL)	80
Milk chocolate bar (9 g)	6
Dark chocolate bar (9 g)	20

After its oral ingestion, the molecule is rapidly absorbed by the gastrointestinal tract, reaching peak plasma concentration in 15 to 60 minutes,[6-8] with a half-life of 2.5 to 10 hours.[8] In moderate doses, caffeine promotes a sense of well-being, reduces fatigue, improves motor skills and increases alertness and attention.[9] However, at higher doses, the drug can cause anxiety, panic attacks, hallucinations, irritability, and can have a negative action on motor control and quality of sleep.5 Moderate consumption (200-300 mg/day) in healthy individuals is not associated with significant adverse effects.[4]

Doses above 600 mg/day are considered excessive and abstinence symptoms can occur after abrupt withdrawal, although these symptoms have been reported even with low-dose consumption (50-150 mg/day).[10] After ingestion of one cup of coffee (approximately 100 mg of caffeine) there is an increase in caffeine levels of 1-2 mg/g in the blood. The lethal blood level is 80-100 mg/g, that would require an intake of at least five grams of caffeine, which suggests a fairly wide range of safety.[7]

Once ingested, caffeine is distributed homogeneously in the different organ systemsincluding the central nervous system (CNS), where it operates by blocking adenosine receptors, mainly the type A1 and A2a.[9] Adenosine, in turn, is a neuromodulator that acts, along with other agents, to reduce nerve conduction velocity.[8]

Thus caffeine, with its antagonistic effect on adenosine receptors, increases this conduction velocity. Among other mechanisms, phosphodiesterase inhibition is attributed to caffeine, as well as the sensitization of ryanodine receptors for calcium release and, finally, GABA receptor antagonism.[3]

Caffeine is metabolized by the liver and excreted by the kidneys with less than 5% being excreted in an unaltered form.[8]

The cervical vestibular evoked myogenic potential (cVEMP) is a short-latency electrophysiological inhibitory potential used for the assessment of the vestibular system through electromyography of the sternocleidomastoid muscle evoked by sound stimuli, bone vibration or electrical stimulation. This test has been used in practice to evaluate the vestibulocollic reflex (VCR) and assess the integrity of the sacculo-collic pathway: saccule, inferior vestibular nerve, vestibular nucleus, medial vestibulo-spinal pathway, nucleus and accessory nerves and sternocleidomastoid muscle.[11-14]

The cVEMP exhibits a biphasic waveform, of which the first peak is positive and called p13, and the second peak is negative, and called n23. Three main parameters are evaluated: p13, n23and p13-n23 amplitude. The latter should be measured not as an absolute value, but as a relative value compared to the contralateral side or the ipsilateral side in different moments.[15] This is because the absolute values of p13-n23 vary according to the degree of muscle contraction, to the conduction and placement of the electrodes and the to the intensity and frequency of stimulus presentation.[11,16,17]

The literature shows increased cVEMP amplitude after the administration of furosemide and glycerol in patients with endolymphatic hydrops.[18-20] This is objectively determined by the calculated change index (CI).

The objective of the present study is to assess the actual effect of caffeine on the sacculo-collic pathway through cVEMP, measured at two different times.

Subjects and methods

Sample selection

A total of 25 young healthy adult subjects were selected as a convenient sample. The volunteers underwent a detailed history and general and specific physical examination. They had abstained from caffeine for at least 24 hours prior to the assessment.

The sample was categorized according to age and gender and daily caffeine intake. The exclusion criteria were cochlear diseases; medications that interfere with the vestibular system; migraine crises, hypertension, dyslipidemia, endocrine diseases including diabetes mellitus, hepatic, gastric or renal disorders and sleep disturbances.

Drug administration

Caffeine was administered in capsules, which give a more rapid and controlled peak effect compared to coffee and cola-derived drinks in the same concentration; the peak of drug action occurs in approximately 60 minutes.[21] Two capsules with 210 mg of pure caffeine were given to every individual undergoing clinical study, for a total dose of 420 mg. This dose is sufficient to reach the plasma concentrations necessary to block adenosine receptors, promoting the expected stimulating effects, but without causing significant side effects.[9]

Test

The cVEMP was performed using a Nihon-Kohden evoked potential response unit, Neuropack MEB-5504K model, installed in an environment with electric and acoustic insulation. The tests were performed by placing ear-bud type earphones in each ear and three electrically isolated surface electrodes, fixed with electrolytic conduction glue in the transition between the upper and middle thirds of the right and left sternocleidomastoid muscle (inverted electrodes - negative) and one inch below the sternal notch on the manubrium of the sternum (not inverted electrode - positive). The maximum impedance permitted for the measurement was five Kohms.

Each volunteer was placed in the supine position on a 180-degree reclining chair and was asked to performed head flexion at approximately 30° during the presentation of the sound stimulus, so that the sternocleidomastoid muscle remained contracted at the moment of recording.

A narrow-band tone-burst stimulus was given at an intensity of 100 decibels sound pressure level at a frequency of 1000 Hertz. The presentation rate was five Hertz. Two binaural measurements were performed, with an interval of two minutes between them to allow the patient to rest; 200 stimuli were averaged in each of these measurements.

The electromyography of sternocleidomastoid muscle was obtained using a low-pass filter of 1000 Hz and 10 Hz high-pass, with artifact rejection, represented in a window of 50 milliseconds. Thus the biphasic complex response was obtained, of which the first positive deflection was called p13 and the first negative deflection was called n23.

Three main measurements were made in absolute values: latency for the p13 wave, latency for the n23 wave (both in milliseconds) and p13-n23 amplitude (in microvolts). After analysis of these data, p13 and n23 latencies were compared before and after drug ingestion. The formula shown in Figure 1 was used for the comparison of the p13-n23 amplitude before and after caffeine ingestion; it is widely used in studies that compare cVEMP before and after the intake of other drugs such as furosemide and glycerol,[15,19,20] since there is a significant individual variation in the absolute value of the p13-n23 amplitude.

However, it was necessary to determine the normal range of this index. To do that we assumed that the right and left ears of each individual were symmetrical and used the formula shown in Figure 2 for the calculation of the asymmetry index (AI) in control tests, determining that the mean plus two standard deviations was the maximum value allowed as asymmetry.[15,19,20] The values were described in module.

$$CI = \left| \frac{amplitude\ ear\ x\ before - amplitude\ ear\ x\ after}{amplitude\ ear\ x\ before + amplitude\ ear\ x\ after} \right| \times 100$$

Figure 1 Change Index (CI).

$$AI = \left| \frac{amplitude\ right\ ear\ - amplitude\ left\ ear}{amplitude\ right\ ear\ + amplitude\ left\ ear} \right| \times 100$$

Figure 2 Asymmetry index (AI).

Study design

This is an historical cross-sectional cohort study, approved by the institutional Research Ethics Committee, under the number 0127/11. All the 25 participants received explanations regarding all procedures to be performed and signed the free and informed consent form.

The volunteers were instructed to abstain from caffeine for at least 24 hours prior to the test.

Two tests were performed on each of the subjects with a mean interval of 60 minutes. After the first test, the individuals received two capsules containing pure caffeine (210 mg / capsule) with 100 mL of filtered water to help deglutition.

Normal values of p13, n23, p13-n23 amplitude and AI were obtained from the tests prior to drug ingestion and these values were compared to those obtained in tests after caffeine ingestion to assess the drug influence on the electrophysiological response capture.

To prevent analysis bias, the examiner did not know whether an examination was performed before or after drug administration.

Statistical analysis

Descriptive data analysis was performed, as well as the non-parametric comparison between groups before and after drug administration.

Numerical data are shown as mean and standard deviation (SD) and categorical data as percentages. Wilcoxon test was used to compare the groups before and after caffeine administration. The level of significance was set at $p < 0.05$.

Results

The sample consisted of 68% female and 32% male subjects. The mean age of the volunteers was 29 years, ranging from 25 to 37 years. The mean daily caffeine intake was 148 mg, ranging from 0 to 500 mg.

A comparative analysis of data from the right and left ears at the tests before administration of caffeine, which included p13 and n23 latencies and p13-n23 amplitude, showed no statistical difference between the sides. Thus, we assumed that there is no difference between sides and the groups were joined and analyzed as a single group of 50 ears. To determine the threshold value of the interpeak amplitude, we considered n = 25, as the AI is only possible between the sides. The normal values are shown in Table 2.

When applying the Wilcoxon test for paired samples, it was observed that there was no statistically significant difference between the tests before and after the use of caffeine, with respect to the p13 and n23 latencies, as well as the p13-n23 amplitude (Table 3).

Table 2 Normality values.

	Mean	SD	n
p13	13.41	1.27	50
n23	23.24	2.74	50
IA	14.20%	6.97%	25

Table 3 Comparison between tests.

		Pre	Post	p
p13	Mean	13.41	13.56	0.248
	SD	1.27	1.39	
	n	50	50	
n23	Mean	23.24	23.14	0.546
	SD	2.74	2.71	
	n	50	50	
Amplitude p13n23	Mean	71.90	76.82	0.170
	SD	47.85	48.22	
	n	50	50	

It was observed that the AI considered normal for the test conditions was 28% (mean + 2SD). Thus, when comparing the Change Index (CI), it was observed that no ear had a higher index than the normal standard value of 28%.

Discussion

Caffeine is a neuromodulator widely used by the world's population. It has been implicated in a number of effects, which mainly involve the CNS, through the inhibition of adenosine receptors.

The data found in the literature and otoneurological clinical experience show adverse clinical effects from caffeine, with significant improvement in symptomatic patients with a gradual reduction in consumption; sudden drug cessation can lead to withdrawal symptoms.[5,10] For example, in patients who are caffeine users and have a diagnosis of vestibular migraine, it has been suggested that caffeine discontinuation is essential for clinical improvement.[22]

Considering this information, one would expect to find some kind of alteration in patient examination after caffeine ingestion, since caffeine causes vestibular symptoms. However, by analyzing the data obtained when comparing the 50 ears before and after drug administration, no significant differences were found in latencies and amplitudes of the waves, with the CI remaining within normal limits. (< 28%).

After ingestion of 300 mg of caffeine, there is an increase of 30 micromoles of the drug in blood plasma,[9] so the ingestion of 420 mg of the substance should increase the plasma level at least to that value. At these plasma levels, caffeine acts primarily on adenosine receptors,[23] having little or no influence on calcium, phosphodiesterase and GABA.[9,24] Therefore, at the dose used, one should expect some significant action on adenosine receptors. To obtain an effect on the other physiological mechanisms, one would need a much higher plasma drug level, which would exceed the toxic dose of caffeine. Therefore, we did not consider the possible effects on these mechanisms for purposes of the present study.

The distribution of adenosine receptors varies according to their type. The A1 receptors are located throughout the brain, but are mainly concentrated in the hippocampus, cerebral cortex, cerebellum and hypothalamic nuclei. The A2a receptors are concentrated in the striatum, and its main role is attributed to dopamine modulation.[8,25,26] The cVEMP is a short latency potential that evaluates the integrity of the sacculo-collic pathway, which includes the saccule, inferior vestibular nerve, vestibular nucleus, vestibulospinal tract, nucleus and accessory nerve and sternocleidomastoid muscle, and is a reflex strictly ipsilateral to the stimulus.[12] Thus, there is no localization of adenosine receptors with the studied sacculo-colic pathway.

After the ingestion of 3 mg/kg of caffeine in humans, the auditory brainstem evoked potential showed a statistically significant reduction in latencies of waves IV and V and a tendency for a reduction in the amplitudes of waves I, II and III, that was not statistically significant . Evaluating middle latency auditory potentials, after caffeine ingestion revealed even more significant results,[9] demonstrating that

adenosine receptors have a greater influence at the central level than at the periphery.

The vestibular nuclei both receive and emit nerve impulses to the central and peripheral organs. Thus, the vestibular nuclei connect with the oculomotor nuclei, medial longitudinal fasciculus, medial and lateral vestibular spinal tract, cerebral cortex, cerebellar peduncle and the vestibular commissural system, autonomic nervous system and the thalamus.[27] As previously mentioned, the presence of adenosine receptors in these central vestibular pathways has been documented. Thus, we believe these numerous connections of the vestibular nuclei with the other central pathways could lead to the deleterious effects of caffeine in several peripheral vestibular pathways, even if the latter did not have adenosine receptors.

Although the administered dose of caffeine was enough to act on adenosine receptors, there were no alterations in any of the test parameters in the study model, which leads us to infer that these receptors are absent or show a reduced presence in the sacculo-collic pathway. That suggests that there is a negligible influence of adenosine receptors on the sacculo-collic pathway and further studies are necessary to clarify the distribution of these receptors in the peripheral vestibular pathways. In addition, the study subjects had no diagnosed vestibular dysfunction, which does not rule out the possible occurrence of caffeine influence on vestibular pathway disorders.

However, this does not invalidate the influence of caffeine on the vestibular system, which consists of several other peripheral and central structures, as described.

Conclusion

We conclude that there was no statistically significant difference in cVEMP in young adults after ingestion of 420 mg of caffeine in the studied model, which shows little influence of caffeine on the examination.

Conflicts of interest

The authors declare no conflicts of interest.

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