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Stimulus Expectancy and Stimulus Response of Caffeine on 4-km Running Performance: A Randomized, Double-blind, Placebo-controlled and Crossover Study

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ABSTRACT

International Journal of Exercise Science 15(2): 645-654, 2022. The placebo effect of caffeine has been poorly investigated in endurance exercise. Therefore, the aim of this study was to analyze the placebo effect of caffeine on 4 km running performance in amateur runners. Twenty-two healthy and recreational male runners (25.5 ± 8.4 yrs; 75.0 ± 7.1 kg; 173.7 ± 6.3 cm) underwent a deceptive experimental design consisting of three different sessions: a) control (CON) in which participants did not ingest any substance; b) placebo (PLA) in which participants ingested a capsule filled with maltodextrin but they were informed that they would receive caffeine; c) caffeine (CAF) in which participants were informed that they would receive caffeine and actually received caffeine. After 60 min for substances absorption, participants performed a 4-km test and they completed the distance as fast as possible. The time employed to cover the distance was lower in PLA (17.4 ± 1.5 min) and CAF (17.4 ± 1.4 min) than CON sessions (18.6 ± 2.8 min; $P<0.05$). There were no differences in the 4-km times between PLA and CAF ($P>0.05$) and no differences were reported between treatments for RPE ($P>0.05$). In conclusion, there was a placebo effect of caffeine on a 4-km maximal running trial which entailed that believing to have ingested caffeine improved performance to a similar extent than actually receiving caffeine. Therefore, the expectancy induced by caffeine may be one of the mechanisms behinds the ergogenic effect of this stimulant on endurance exercise.

KEY WORDS: Ergogenic resource, running, physical performance, caffeine

INTRODUCTION

Caffeine has been widely used to increase performance in both aerobic and anaerobic activities (3,12). The action of caffeine to increase performance can be mainly explained by central mechanisms (i.e., increase in cortical and spinal excitability, and enhanced release of neurotransmitters that produce augmented muscle fiber conduction velocity and motor unit

recruitment (14). Specifically, caffeine has the capacity to blunt the fatiguing effects of adenosine on the central nervous system through its antagonism on adenosine receptors A_1, A_{2A} and A_{2B} of various tissues (8). Therefore, when caffeine is ingested acutely in a dose of 3-to-9 mg/kg of body mass, this stimulant delays fatigue during exercise (8), enhances performance (11) and decreases the rate of perceived exertion in both resistance and dynamic aerobic exercises (2). Additionally, caffeine can produce peripheral changes, such as the increase in intracellular calcium concentration (10), the attenuation of potassium ion concentration (16) and enhanced muscle oxygenation in active muscles (20) that may contribute to its ergogenicity.

The ergogenic effect of caffeine appears to occur regardless of dose and time of ingestion (24). However, there are recent data suggesting the possibility of a placebo effect associated to caffeine on exercise performance (1,4,23). The placebo effect of caffeine can be defined as a psychobiological response, mainly displayed as an increase in physical performance or feelings of performance, that arises from the belief that caffeine has been ingested when in fact, the participant has received a placebo (13). This effect can be explained by the fact that response expectancy (if the participant believes he/she ingested caffeine and he/she is aware that caffeine is a potent ergogenic substance that may increase performance) promotes the endogenous release of opioids and non-opioids, facilitating the activation of pain and non-pain control systems (7). Interestingly, this effect is associated to caffeine because it is a substance with a well-recognized ergogenic effect and, due to its wide consumption in the diet, most individuals have experienced the effect of acute caffeine intake. In this context, the psychophysiological variables induced by the believe of caffeine ingestion (motivation, expectancy, and conditioning) can interact significantly with physiological variables such as muscle activation of motor units or reduced pain and effort acting positively -or negatively- on exercise performance (5).

The relationship between the placebo effect of caffeine and enhanced physical performance has been documented in the literature (4,13), although this is not always the case (25). To this regard, most studies on the placebo effect of caffeine have been performed using randomized, double-blind, placebo-controlled, crossover designs but the deceptive protocols contain substantial differences. Overall, the deceptive protocols contain a trial where participants are informed of receiving an ergogenic dose of caffeine when in fact, they received a placebo. Exercise performance in this trial is normally compared to a trial where participants actually received caffeine, although more complex experiments have arisen in the last years (1,25). However, the ergogenic effect of caffeine is not only explained by its placebo effect as most of experiments with caffeine use a placebo trial to eliminate this effect (21) and there are evidence indicating that verified differences between the psychological and physiological effect of caffeine. For example, Polito et al. (18) verified the effect of two doses of caffeine on the performance of resistance exercise, while the sample believed that one of the doses was placebo. Even though the sample believed they ingested a placebo, performance was higher than in the control session (without substances).

Studies with these deceptive designs are still relatively scarce in the literature, especially the ones that investigate the placebo effect of caffeine on endurance exercise. It may be worthwhile

analyzing the potential psychological effect of believing to have ingested caffeine on physical performance, through deceptive protocols, to ascertain if this is a mechanism that contributes to the ergogenic effect of actual caffeine intake. Thus, the aim of this study was to investigate the existence of a placebo effect of caffeine on 4 km running performance in amateur runners.

METHODS

Participants

An a priori power analysis using statistical software (G*power V 3.1.9.4) was completed to determine an adequate sample size. Thus, 22 healthy male runners volunteered to participate in this study, depicted in Table 1. As inclusion criteria, individuals were required to be aged between 18-40 years of age, have a minimum of six months of endurance running training, have no injuries in the lower limbs in the previous six months, no respiratory or cardiovascular diseases, low-to-moderate caffeine consumption (< 2-3 cups of coffee) and no allergy to caffeine. Participants who were undergoing restrictive diet control or were using stimulants and nutritional supplements were excluded from the study. Participants were encouraged to maintain a normal diet and exercise habits throughout the duration of the study, and they were asked to abstain from caffeine intake for the duration of the study, and to refrain from vigorous exercise for at least 48 hours prior to testing. Participants signed an informed written consent prior to participating in the investigation where they were fully informed of the experimental procedures and risks. Informed consent was obtained from each participant before data collection and all experimental procedures were approved by the Research Ethics Committee Involving Humans of the State University of Londrina. This research was carried out in accordance with the ethical standards of the International Journal of Exercise Science (17).

Table 1. General characteristics of the sample (n=22).

Variables	Mean
Age (years)	25.5±8.4
Weight (kg)	75.0±7.1
Height (cm)	173.7±6.3
Body fat (%)	19.9±4.4
Sleep (hours/day)	8.2±0.5
Usual running training per day (km)	5.5±2.6
Daily coffee consumption (ml)	346.5±198.2

Protocol

Following a deceptive, randomized, double-blind, placebo-controlled, and crossover experimental design, data collection was performed on three non-consecutive trials with a minimum interval of 72 h. Participants performed a maximum test consisting of the completion of a distance of 4 km running while participants were encouraged to complete this distance in the lowest time possible. Participants performed this test in three different conditions: a) control (CON) in which participants did not ingest any substance; b) placebo (PLA) in which participants ingested a capsule filled with maltodextrin but they were informed that they would receive 4 mg/kg of caffeine; c) caffeine (CAF) in which participants were informed that they would really receive 4 mg/kg of caffeine. In PLA and CAF, the capsules were identical, and they

were ingested 60 min before the onset of the 4-km test. To avoid possible interferences of the time of the day on the outcomes of the investigation, the trials were performed in the afternoon (2 pm) and in a laboratory with well-controlled ambient conditions (~22ºC and ~60% of relative humidity).

Once participants fulfilled all the inclusion criteria and signed the informed consent, they were encouraged to avoid any type of caffeine-containing foods and beverages until the completion of the experiment (e.g., coffee, tea, chocolate, etc.). One week before the onset of the experiment, participants arrived to the laboratory to familiarize with the experimental procedures and they were weighed unclothed at this day to calculate caffeine dose for the CAF trial. In this session, participants were informed about the findings of research related to acute effects of caffeine intake on endurance exercise performance through informal conversations that included information about the ergogenic effect of caffeine, dosage and most common side effects. Then, the participants were instructed to meet the following conditions 24-h before each experimental trial: (i) to avoid vigorous exercise, (ii) to adopt a similar diet and drink intake, (iii) to refrain from the consumption of alcohol, and other stimulants (iv) to sleep at least 8 h in the night before the tests. In the experimental trials, participants arrived at the laboratory in a fed state (~3 hours after their last meal). Upon arrival, participants ingested the capsule in the PLA and CAF trials and rested for 60 min. In the CON trial, participants ingested for the same duration but there was not capsule ingestion. Afterwards, participants performed a 10-min standardized warm-up and then they performed the 4-km running test.

The running test was performed on an electrical treadmill set with a slope of 0%. The speed of the treadmill was progressively increased until it reached the speed desired for the participants and then the test started. Individuals were encouraged to run the distance as fast as possible in the shortest possible time and standardized verbal motivation was given. Participants were able to control the speed during the whole trial through an accessible dashboard, they received information about the distance left to complete the trial but there was no information of the actual speed and the time employed since the beginning of the trial. During the test, times and rating of perceived exertion (RPE) were recorded every 1 km using the 6-to-20-point Borg Scale (6). This information was collected by an investigator who was blinded to the treatment assigned to each participant. After the end of the test, participants performed a 3-min cool-down period at 5 km/h and they were discharged.

Statistical Analysis

The normality of the data was verified by the Shapiro-Wilk test and the homogeneity of variances by the Levene test. Given the assumptions of normal distribution, two-way ANOVA was applied to verify the effect of CON, PLA, and CAF on the times to complete each 1-km interval during the test and on the total 4-km running time. The same procedure was used to verify the results in the RPE. Tukey's post-hoc tests were used in the case of a significant F test. In all cases, a p-value less than 0.05 was considered as the level of statistical significance. Additionally, to determine the magnitude of the findings, Cohen's d effect sizes (ES) were calculated for the differences between PLA and CAF, following the classification: small

(0.20<ES<0.50), medium (0.50≤ES<0.80) or large (ES≥0.80). The data were analyzed using the software Statistica 10.0 (Statsoft, Tulsa, OK, USA). Data are presented as means ± standard deviations.

RESULTS

Table 2 shows the total running time and the running pace for the 1st, 2nd, 3rd, and 4th km of each trial. The intra-session analysis demonstrated that the pace per kilometer tended to increase in CON (P=0.03), to decrease CAF (P=0.02), and remain constant in the PLA (P=0.75). In CON, the pace of the 1st km was slower than the 2nd km (P=0.03); the pace of the 2nd km was faster than the 3rd km (P=0.01) and the 4th km (P=0.02); and the pace of the 3rd km was faster than the 4th km (P=0.04). In CAF, the pace of the 1st km was slower than the 2nd (P=0.02), 3rd (P=0.02) and 4th km (P=0.02). The inter-session comparisons showed that the pace of the 1st km of PLA was quicker than that of the other two trials (P=0.02). In the 2nd km there were no differences among the three trials. In the 3rd km, only CAF was quicker than CON (P=0.01); and in the final kilometer, both PLA and CAF presented faster paces than the CON session (P=0.02; P<0.01, respectively). PLA and CAF conditions were similar in relation to the total time but participants employed a lower total time compared to CON in these two trials (P=0.03; P=0.01, respectively).

The ES for all inter-session and intra-session comparisons at running pace was considered small (ES<0.50). For the total running time, the ES was considered medium both in the PLA vs CON (ES=0.53) and CAF vs CON (ES=0.54) comparison.

Table 2. Total time and pace per kilometer (in minutes) in the different sessions.

	Pace per kilometer				Total time
	1st km	**2nd km**	**3rd km**	**4th km**	**4 km**
CON	4.7±1.0	4.4±0.6[1]	4.6±0.6[2]	4.9±1.3[2,3]	18.6±2.8
PLA	4.3±0.4[#]	4.3±0.5	4.4±0.6	4.4±0.6[†]	17.4±1.5*
CAF	4.6±0.5	4.4±0.4[1]	4.2±0.5[1‡]	4.2±0.5[1†]	17.4±1.4*

Numbers represent intra-group comparisons: 1 = Different from the 1st km of the same session; 2 = Different from the 2nd km of the same session; 3 = Different from the 3rd km of the same session. Symbols represent inter-group comparison: * Different from the total time of the control session; † Different from the 4th km of the control session; ‡ Different from the 3rd km of the control session; # Different from the 1st km of the control session and from the 1st km of the caffeine session. All differences were set at $p < 0.05$.

Table 3 describes RPE values obtained every 1 km intervals in the three situations under investigation. Although the RPE increased throughout the test in all trials there were no significant differences among the treatments. In all cases, the ES was small (ES<0.40).

Table 3. Rating of perceived exertion every 1 km.

	Rating of perceived exertion			
	1st km	**2nd km**	**3rd km**	**4th km**
CON	12.9±1.7	13.9±1.2[1]	14.7±1.4[1]	15.1±1.9[1]
PLA	12.8±1.4	14.1±1.2[1]	15.3±1.4[1]	15.4±1.8[1]
CAF	12.1±1.6	13.8±1.2[1]	14.9±1.4[1]	15.8±1.5[1,2]

Numbers represent intra-group comparisons. 1 = Different from the 1st km; 2 = Different from the 2nd km. All differences were set at $p < 0.05$.

DISCUSSION

The aim of this study was to investigate the existence of a placebo effect of caffeine on 4 km running performance in amateur runners to demonstrate the utility o the expectation of ingesting caffeine as an ergogenic tool to enhance performance. The main results of the study were: a) there was a placebo effect of caffeine, since the real intake of caffeine and the expected ingestion of caffeine increased running performance to the similar extent when compared to the control session; b) there were no differences in RPE between sessions indicating that participants performed the trials with the same feelings of exertion. These outcomes suggest that believing to have ingested caffeine improved running performance to a similar extent than actually receiving caffeine. Therefore, the expectancy induced by caffeine may be one of the mechanisms behinds the ergogenic effect of this stimulant on endurance exercise.

The construct used in the present study including a deceptive design in which participants were informed that caffeine would be offered on two days to determine the consistency of the ergogenic effect of caffeine. However, on one day, the capsule ingested contained a placebo and in the other day, the capsule contained 4 mg/kg of caffeine. This procedure was applied to avoid bias of motivation, as this design prevented that if the subject believed that caffeine was ingested on the first day he would not be less motivated for the second day. In this context, the perception of the ingested substance can be an important factor related to enhanced performance, particularly for caffeine's erogenicity. For example, Saunders et al. (12) used caffeine and placebo, in comparison to a control situation, to assess performance in trained cyclists during a 30 min cycling trial. Afterwards, the cyclists were were asked about which supplement they believed they had ingested ("caffeine", "placebo", "don't know") and they were allocated to subgroups for analysis according to their identifications. Interestigly, the results showed that the actual ingestion of caffeine enhanced cycling performance but in those cyclists who correctly identified the trial with caffeine, the ergogenic effect of this stimulant was slightly higher. In addition, there was a tendency for a better over the control situation when they ingested placebo but they believed that it was caffeine. On the other hand, Beedie et al. (4) informed cyclist that they would receive one dose of placebo and two doses of caffeine, whereas, in fact, the authors provided three placebo substances. The results showed that performance improved when athletes believed they had ingested caffeine and worsened when they believed they had ingested placebo. In another experiment, in which individuals received placebo while they were told they had received caffeine, similar results were observed in 1000-m running performance when compared to a situation where they received caffeine (14). The current results study to this

topic as the placebo effect of caffeine was found on a 4-km running test. All these results suggest that both, the actual ingestion of caffeine and the believe of ingesting caffeine are independent parts of the ergogenic effect of this substance. To this regard, the presence of one factor (actual ingestion or the believe of ingestion) has the potential of increasing performance but the combination of these two likely offers an additive effect.

In the current study, participants believed they had ingested caffeine at two trials, which may have contributed to the improve performance when they in fact ingested the placebo. This can be explained by two hypotheses. Firstly, some subjects may experience side effects in relation to caffeine intake, and some of these side effects may occur even after taking the placebo (if the subject believes they have ingested caffeine). Secondly, another factor that could have contributed to the placebo effect of caffeine is the "feeling" of performance during the trial (such as perception of speed or pace). Thus, an expectation of response can be generated, in which the participant feels more motivated to impose more effort in relation to the session, even when they had ingested an inert substance. This is only applicable to substances who are ergogenic and to individuals who are aware to the ergogenic effect of this substance as the deceptive protocol and the placebo effect will not be produced in those individuals who are not aware of the benefit of caffeine. To this regard, participants in the current investigation were selected due to their low-to-moderate consumption of caffeine, to assure that they have experience and knowledge about the effect of caffeine during exercise while they were informally lectured about the findings of research related to acute effects of caffeine intake on endurance exercise.

One physiological justification for this finding of this study that the expectancy of caffeine intake may promote the endogenous release of opioids and non-opioids, facilitating the activation of pain and non-pain control systems (7). This was verified in a study in which a false placebo was administered in a resistance exercise protocol, when in fact received a dose of caffeine (18). In the present study, participants were blinded in relation to speed and time during each trial and thus, they did not receive any objective information to anticipate their performance. However, as the sample had running experience, it is possible that their perception of the pace influenced the result of the ingestion of the placebo, at least in relation to the control situation. Thus, psychophysiological variables, such as motivation, expectation, and conditioning can interact with physiological variables, such as muscle mass and activation of motor units, acting positively on performance (5). These explanations seem to be centered on the OPTIMAL theory, that is, Optimizing Performance Through Intrinsic Motivation and Attention for Learning (26). According to this model, the increase in expectations, support for autonomy, and external focus influence performance and motor learning. Thus, the supposed relationship of these reward factors provides an increased dopaminergic response, triggering better performance and building structural and functional brain connectivity.

In addition to the total time of the 4-km run, there was carried out an analysis of the pace for each kilometer covered. Curiously, in the control session, the pace of the run was progressively reduced while the reduction in running performance was not seen in the other two treatments. This suggests that the second half of the run was decisive for the results and both, the ingestion

of caffeine and the believe of receiving it were equally effective to reduce fatigue in the second half of the 4-km run.

Regarding the interaction of caffeine with RPE, the results of the meta-analysis by Doherty and Smith (9) suggest that caffeine intake decreases RPE by 5.6%. However, our results did not identify differences in RPE between sessions. One of the possible explanations for this divergence is that the subjects were instructed to run the distance in the shortest possible time, thus characterizing maximum effort in all sessions. Therefore, in spite of the reduced time in the PLA and CAF sessions, the high level of physical demand prevented any change in the RPE, as participants exerted their maximum effort in all trials. Similarly, Astorino et al. (2) did not identify differences in RPE in a 10-km time trial when comparing caffeine intake and placebo. In addition, RPE during exercise is multifactorial and, ultimately, may not be related to physical performance (22).

Although the results were positive for the adopted experimental design, we understand that the study has some limitations. For example, the diet in the day prior to the trials was not standardized. However, the analysis of the dietary recall did not identify any differences in the energy intake nor in macronutrients proportions among trials. In addition, the duration of the 4-km run was likely not enough to produce influence of glycogen depletion on the results of the investigation. Second, the sample of individuals included in this investigation had a low-to-moderate intake of caffeine. Further investigations are necessary to indicate if the placebo effect of caffeine is affected by the habituation of caffeine as in those athletes highly habituated to caffeine, the use of this type of deceptive experiments may not be successful. In addition, tolerance to the ergogenic effect of caffeine may affect the placebo effect of caffeine due to both reduction of the positive and negative effects of this substance (15,19). Finally, the experimental design could have included a broader approach, covering a real placebo condition and a caffeine ingestion condition with a placebo expectation. Thus, in the face of a scenario where new investigations can be conducted using different ranges of intensity and volume in the run, we suggest experiments taking into account individual expectations and perceptions about caffeine intake.

In conclusion, there was a placebo effect of caffeine on a 4-km maximal running trial which entailed that believing to have ingested 4 mg/kg of caffeine improved performance to a similar extent than actually receiving this dose of caffeine. Therefore, the expectancy induced by caffeine may be one of the mechanisms behinds the ergogenic effect of this stimulant on endurance exercise. The use of a placebo can be used to increase 4-km running performance in trained men who are aware of the ergogenic benefits of this substance and under a deceptive protocol, representing an alternative to the use of caffeine.

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