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RESEARCH ARTICLE

Effect of caffeine on long-term potentiation-like effects induced by quadripulse transcranial magnetic stimulation

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Abstract

Caffeine, an adenosine receptor antagonist, is known to affect sleep–awake cycles, the stress response, and learning and memory. It has been suggested that caffeine influences synaptic plasticity, but the effects of caffeine on synaptic plasticity in the human brain remain unexplored. The present study aimed to investigate the effects of caffeine on long-term potentiation (LTP)-like effects in the primary motor cortex of healthy humans. Twelve healthy participants (six women and six men; mean age: 44.8 ± 1.5 years) underwent quadripulse magnetic stimulation with an inter-stimulus interval of 5 ms (QPS5) to induce LTP-like effects, 2 h after administration of either a caffeine (200 mg) or placebo tablet in a double-blind crossover design. We recorded motor-evoked potentials (MEPs) before and after QPS5. The degree of MEP enhancement was compared between the placebo and caffeine conditions. Neither active nor resting motor thresholds were influenced by caffeine administration. Following caffeine administration, the degree of potentiation significantly decreased in "significant responders", whose average MEP ratios were greater than 1.24 in the placebo condition. The observed reduction in potentiation following caffeine administration is consistent with the A_{2A} receptor antagonistic effect of caffeine. This is the first report of an effect of caffeine on neural synaptic plasticity in the human brain, which is consistent with the caffeine-induced plasticity reduction observed in primate studies. Because we studied only a small number of subjects, we cannot firmly conclude that caffeine reduces LTP in humans. The present results will, however, be helpful when considering further or new clinical uses of caffeine.

Keywords Cortical plasticity · Non-invasive brain stimulation · Dopamine · Adenosine · Parkinson's disease

Introduction

Caffeine is a widely consumed psychoactive drug and affects sleep–awake cycles, the stress response, and learning and memory. Pharmacologically, caffeine functions as a non-selective adenosine A_1 and A_{2A} receptor antagonist (Daly et al. 1983; Fredholm et al. 1999), although it exhibits higher affinity for A_{2A} than A_1 receptors (Ciruela et al. 2006). In the hippocampus, selective A_1 receptor antagonists facilitate long-term potentiation (LTP) (Costenla et al. 1999), whereas selective A_{2A} receptor antagonists attenuate LTP (Fontinha et al. 2006; Rebola et al. 2008; Costenla et al. 2011). However, the effects of caffeine on synaptic plasticity have not been well studied in human or in animal experiments.

Recently, istradefylline, an adenosine A_{2A} receptor antagonist, has been proposed as a new anti-parkinsonian drug (Mizuno et al. 2013). In addition, several reports indicate that caffeine may also improve Parkinsonian symptoms (Altman et al. 2011; Postuma et al. 2012), and that coffee consumption may have protective effects against the development of Parkinson's disease (PD) (Schwarzschild et al. 2002). Furthermore, anti-parkinsonian effects of caffeine have been observed in rat PD models (Herrera-Marschitz et al. 1988, Machado-Filho et al. 2014), which may be explained by the A_{2A} antagonistic effect of caffeine. The A_{2A} antagonist is thought to act as an activator of dopamine

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receptor 2 (D2) in the basal ganglia (Chen 2017). However, it is not clear whether the effects of caffeine or A_{2A} antagonists on neural plasticity are similar to those of D2 agonists. The present study thus aimed to elucidate the effects of caffeine on cortical plasticity in the human primary motor cortex.

A number of non-invasive brain stimulation (NIBS) techniques, such as paired associative stimulation (PAS), theta-burst stimulation (TBS), and transcranial direct-current stimulation (tDCS), induce neural plasticity-like effects in the human primary motor cortex (M1) (Ziemann et al. 2008). Furthermore, levodopa modifies long-term potentiation (LTP) and depression (LTD)-like effects induced by NIBS in healthy participants (Thirugnanasambandam et al. 2011; Monte-Silva et al. 2010; Enomoto et al. 2015). Previously, we reported that levodopa enhances LTP/LTD-like effects induced by quadripulse transcranial magnetic stimulation (QPS), whereas pramipexole—a D2 dominant agonist—had no influence on them (Enomoto et al. 2015). These results are compatible with the dopamine influences on cortical plasticity reported in animal experiments (Guo et al. 2015). In the present study, we investigated the influence of caffeine on LTP-like effects induced by QPS in healthy volunteers.

Methods

Participants

We asked a temporary employment agency to recruit participants who were around 45 years of age. The following exclusion criteria were used, in line with common safety guidelines (Wassermann 1998; Rossi et al. 2009): people with gastric or duodenal ulcers; individuals carrying metal devices such as a cardiac pace maker, a drug delivery pump, or deep brain stimulation electrodes; individuals with severe cardiac disease, hepatic disease, renal disease, pulmonary disease, ileus, bronchial asthma, uncontrolled diabetic mellitus, chronic open angle glaucoma, cerebral stroke, brain injury, brain tumors, epilepsy, or psychiatric disorders; pregnant women and those contemplating pregnancy; and people whom the investigators considered inappropriate for participation. None of the participants had any history of neurological or psychiatric diseases or seizure episodes. Participants were not taking any medications for neurological or psychiatric diseases before and during the experiments, and they did not consume caffeine on the experimental day. The agency recruited 7902 people, and of these, 69 applied for the current study. Four individuals were excluded based on the exclusion criteria, while the other 65 applicants were considered candidates for selection. As this was a pilot study, we examined only a small number of subjects. Twelve individuals [six men and six women; mean age: 44.8 ± 1.4 years (mean ± SD)] were thus randomly selected from the 65 applicants and participated in the present double-blind, complete crossover, placebo-controlled study.

The present study was conducted in accordance with the Declaration of Helsinki, and all procedures were approved by the Institutional Review Board of the University of Tokyo (No. P2012004, UMIN000008508). All subjects provided written informed consent before participation in this study.

Transcranial magnetic stimulation

Participants sat in a comfortable chair. Surface EMG was recorded from the right first dorsal interosseous muscle (FDI) using surface electrodes placed with a belly–tendon montage filtered between 100 and 3 kHz (Multi Amplifier 1000, DIGITEX LAB Co. Ltd., Japan or Biotop; GE Marquette Medical Systems Japan Inc., Japan). TMS was applied on the left motor cortex (M1) with a figure-8-shaped magnetic coil (7 cm external diameter at each wing; The Magstim Company Ltd., UK) connected to a TMS machine (Magstim 200, The Magstim Co. Ltd., UK). Active motor threshold (AMT) was defined as the intensity required to elicit five MEPs of at least 100 μV in active muscles, while resting motor threshold (RMT) was defined as the intensity required to elicit five MEPs of at least 50 μV in relaxed muscles, over 10 consecutive trials. TMS intensity was fixed to elicit MEPs of approximately 0.5 mV in relaxed muscles.

Quadripulse stimulation for LTP induction

QPS was applied over the left M1 with a figure-8-shaped coil through a special combining module (The Magstim Co., Ltd.) connected to four monophasic magnetic stimulators (Mastim 200 square; The Magstim Co., Ltd.). As described in a previous study (Hamada et al. 2008), the QPS consisted of bursts of four monophasic subthreshold TMS pulses repeated every 5 s for 30 min (360 bursts). The stimulus intensity of QPS was set at 90% of the AMT. We used an inter-stimulus interval of 5 ms (QPS5) to induce LTP-like after-effects (Hamada et al. 2008). During the QPS, the participants were instructed not to fall asleep and to keep arousal, and the experimenter made sure these instructions were followed during the intervention.

Experimental protocol

The participants visited our hospital twice, separated by at least 1 week. At these visits, a single dose of caffeine (200 mg) or placebo substance contained in an identical capsule was administered. One doctor in the Department of Pharmacy made the necessary adjustments to the drug blinding. Another doctor performed the drug blinding, while two other doctors allocated the participants into groups. All

experimenters were blinded to the experimental conditions during the experiments. The order of drug intake and placebo intake conditions was randomized. All experiments started at the same time of the day (9 A.M.). Two hours after administration, we measured RMTs and AMTs for motor-evoked potentials (MEPs) from the right first dorsal interosseous muscle (FDI) evoked by a single pulse of transcranial magnetic stimulation (TMS) over M1. We measured 20 MEPs before QPS and at 5, 10, 15, 20, and 25 min after the termination of QPS. We did not confirm that the participants were blind to the experimental conditions via a questionnaire after the experiments.

Data analysis

To evaluate changes in the excitability of cortical motor neurons, we calculated the ratio of the average MEP size at each time point to the average baseline MEP. Two-way factorial repeated measures analysis of variance (ANOVA) was used to perform statistical comparisons of the effects of the factors Drug (caffeine or placebo) and Time following QPS (5, 10, 15, 20, 25 min).

In addition, we classified participants into "responders" and "non-responders" and compared the caffeine influence between the groups, similar to the approach used in our previous studies (Tanaka et al. 2015, Hanajima et al. 2017). We defined "significant responders" as those with an average MEP ratio (0–25 min) greater than 1.24 and "non-significant responders" as those with an average MEP ratio equal to or less than 1.24, based on the normal range of the MEP size ratio in the sham QPS condition in our previous paper (0.76–1.24) (Nakamura et al. 2016).

Results

One participant felt slight nausea after taking the placebo, but the nausea improved spontaneously without medication. No adverse effects following QPS were noted in any participants.

RMTs, AMTs, and single-pulse stimulation intensities used for MEP recordings did not differ between the placebo ($53.7 \pm 8.8\%$, $31.0 \pm 3.2\%$, and $69.0 \pm 19.7\%$, respectively) and caffeine conditions ($50.0 \pm 7.1\%$, $29.3 \pm 4.1\%$, and $62.0 \pm 18.8\%$) (paired t test; $p = 0.13$, $p = 0.21$, and $p = 0.09$).

Seven participants were classified as significant responders and five participants as non-significant responders based on the results of the placebo condition.

Across all participants, MEP amplitudes were less enlarged in the caffeine condition than the placebo condition, although the difference was not significant [Drug: $F(1, 11) = 2.34$, $p > 0.05$; Time: $F(4, 44) = 0.71$, $p > 0.05$; Drug × Time: $F(4, 44) = 0.282$, $p > 0.05$] (Fig. 1a). In significant responders (n = 7), Drug significantly affected the MEP ratio, but Time did not, and no significant Drug × Time interaction was observed [Drug: $F(1, 6) = 10.2$, $p < 0.05$; Time: $F(4, 24) = 0.43$, $p > 0.05$; Drug × Time: $F(4, 24) = 0.42$, $p > 0.05$] (Fig. 1b). No statistically significant differences were observed with regard to any parameters in non-significant responders [Drug: $F(1, 4) = 4.06$, $p > 0.05$; Time: $F(4, 16) = 1.50$, $p > 0.05$; Drug × Time $F(4, 16) = 0.21$, $p > 0.05$] (Fig. 1c).

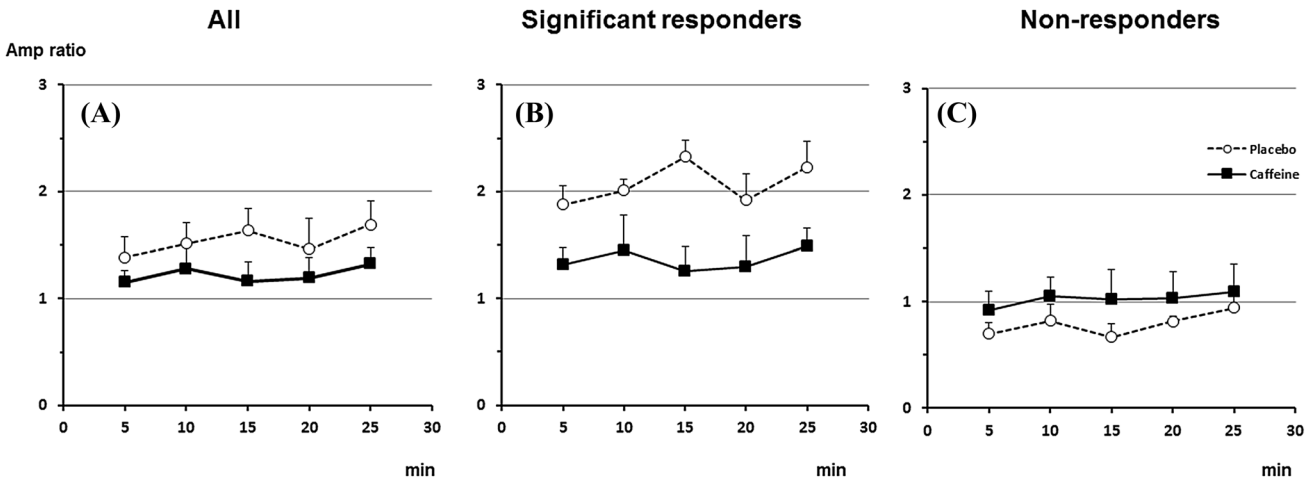

Fig. 1 Time courses of average motor-evoked potential (MEP) ratios after QPS in all participants (**a**), significant responders (**b**), and non-responders (**c**). Circles show the placebo condition and squares show the caffeine condition. *MEP* motor-evoked potential, *QPS* quadripulse transcranial magnetic stimulation

Discussion

In the present study, we observed that caffeine intake decreased LTP-like effects induced by QPS5 in significant responders without any effects on RMTs or AMTs, while there were no effects on LTP in non-significant responders.

Previous studies have reported that caffeine does not affect H-reflex/M-wave amplitudes (Kalmar and Cafarelli 1999), F-wave amplitudes (Cerqueira et al. 2006), or central cortical excitability parameters such as MEP amplitudes, motor thresholds, short-interval intracortical inhibition, or intracortical facilitation (Orth et al. 2005). Effects of caffeine on the cortical silent period have also been investigated. Caffeine was reported to have no influence on the silent period in one study (Orth et al. 2005), while other studies observed that the silent period was shortened by caffeine intake (Cerqueira et al. 2006; de Carvalho et al. 2010). Our results are consistent with these results and indicate that caffeine may affect motor cortical plasticity in humans, without inducing any motor threshold changes.

This is the first report of an effect of caffeine on synaptic plasticity in humans. Only one previous publication has reported that 8.4 oz of a caffeinated energy drink (containing 2.0 mg caffeine/kg) did not affect the degree of LTP induced by PAS (Concerto et al. 2017). The lack of an effect on LTP in this study may be explained by the fact that 2 mg of caffeine was not sufficient to induce plasticity effects. Another possible explanation could be that PAS-induced LTP and QPS-induced LTP have different physiological features. PAS-induced plasticity represents hetero-synaptic plasticity, while QPS-induced plasticity represents homosynaptic plasticity. A few animal experiments have studied effects of caffeine on synaptic plasticity (Costenla et al. 2010; Blaise et al. 2018). Preliminary data (Costenla et al. 2010) from rat hippocampal slices suggested that the degree of LTP decreased following caffeine consumption. Another study reported that caffeine administration over a period of 3 weeks reduced LTP induction in the hippocampus (Blaise et al. 2018). These LTP attenuation effects of caffeine are similar to effects of A_{2A} receptor antagonists (Fontinha et al. 2006; Rebola et al. 2008; Costenla et al. 2011), which suggests that caffeine reduces LTP through A_{2A} receptor antagonistic effects. A_{2A} receptors are distributed in both the basal ganglia and the cerebral cortices, but their distribution is denser in the basal ganglia (Dixon et al. 1996). Thus, based on the above evidence, we speculate that caffeine may reduce cortical plasticity via A_{2A} receptors.

A_{2A} receptors are known to inhibit D2 receptor activation. A_{2A} receptor antagonists, therefore, act as D2 receptor activators. In a previous study (Enomoto et al. 2015), a D2-dominant agonist had no effect on LTP induced by QPS5. Our data show that caffeine had no significant effect on LTP induced by QPS5, which is consistent with the results of our previous study (Enomoto et al. 2015), in which the effect of caffeine was not studied in responders and non-responders separately.

A limitation of this study is the small number of participants, particularly for the separate analyses of responders and non-responders. Future studies with larger numbers of subjects are needed to draw further conclusions on the effects of caffeine on LTP in the human brain. Another limitation is that we did not measure blood levels of caffeine and were thus not able to study the correlation between blood concentration and plasticity. However, we were able to compare the degree of plasticity between the caffeine on and off conditions in the same subjects, and can, therefore, draw conclusions regarding the effect of caffeine on LTP. Moreover, we did not evaluate previous caffeine consumption habits of our participants, and we are not able to speculate how previous consumption habits might have influenced plasticity. Even considering these limitations, however, we could evaluate the effects of caffeine on LTP by comparisons within the same subjects.

Here, we directly show—for the first time—that caffeine may have the potential to attenuate LTP-like effects induced by QPS in the healthy human brain. We hypothesize that this attenuation is likely induced via A_{2A} receptor antagonistic effects, which is consistent with previous results from animal studies. We cannot conclude that LTP is generally reduced by caffeine in humans, because we studied a small number of subjects and only effects on LTP induced by QPS. Nevertheless, the present results suggest that we should be aware of the patient's caffeine intake in a variety of clinical settings. These findings will be helpful when considering further or new clinical uses of caffeine.

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Compliance with ethical standards

Conflict of interest RH received research support from Sumitomo Dainippon Pharma Co., Ltd. and GlaxoSmithKline KK.

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