NeuroImage 110 (2015) 39–47

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Does acute caffeine ingestion alter brain metabolism in young adults?

Feng Xu [a,b,c], Peiying Liu [a,b,d], James J. Pekar [b,c], Hanzhang Lu [a,b,d,*]

[a] Advanced Imaging Research Center, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA
[b] The Russell H. Morgan Department of Radiology & Radiological Science, Johns Hopkins University, 601 North Caroline Street, MD 21287, USA
[c] F. M Kirby Center for Functional Brain Imaging, Kennedy Krieger Institute, 707 N Broadway, Baltimore, MD 21205, USA
[d] Department of Psychiatry, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390, USA

ARTICLE INFO

Article history:
Accepted 26 January 2015
Available online 30 January 2015

Keywords:
Caffeine
Cerebral metabolic rate of oxygen
Cerebral blood flow
Cerebral venous oxygenation
Oxygen extraction fraction
TRUST MRI

ABSTRACT

Caffeine, as the most commonly used stimulant drug, improves vigilance and, in some cases, cognition. However, the exact effect of caffeine on brain activity has not been fully elucidated. Because caffeine has a pronounced vascular effect which is independent of any neural effects, many hemodynamics-based methods such as fMRI cannot be readily applied without a proper calibration. The scope of the present work is two-fold. In Study 1, we used a recently developed MRI technique to examine the time-dependent changes in whole-brain cerebral metabolic rate of oxygen ($CMRO_2$) following the ingestion of 200 mg caffeine. It was found that, despite a pronounced decrease in CBF ($p < 0.001$), global $CMRO_2$ did not change significantly. Instead, the oxygen extraction fraction (OEF) was significantly elevated ($p = 0.002$) to fully compensate for the reduced blood supply. Using the whole-brain finding as a reference, we aim to investigate whether there are any regional differences in the brain's response to caffeine. Therefore, in Study 2, we examined regional heterogeneities in CBF changes following the same amount of caffeine ingestion. We found that posterior brain regions such as posterior cingulate cortex and superior temporal regions manifested a slower CBF reduction, whereas anterior brain regions including dorsolateral prefrontal cortex and medial frontal cortex showed a faster rate of decline. These findings have a few possible explanations. One is that caffeine may result in a region-dependent increase or decrease in brain activity, resulting in an unaltered average brain metabolic rate. The other is that caffeine's effect on vasculature may be region-specific. Plausibility of these explanations is discussed in the context of spatial distribution of the adenosine receptors.

Introduction

Caffeine is the most widely used stimulant drug in the western countries. The primary psychological effects of caffeine are mitigation of drowsiness and improvement in vigilance (Magill et al., 2003). However, the impact of caffeine ingestion on brain physiology is not fully characterized, especially in humans (Chen and Parrish, 2009; Griffeth et al., 2011; Laurienti et al., 2002; Liu et al., 2004; Wong et al., 2012). Caffeine acts through its complex effects on a number of neurotransmission systems such as dopamine, acetylcholine, serotonin, and, in high doses, norepinephrine (Berkowitz and Spector, 1971; Berkowitz et al., 1970; Ferre, 2010; Nehlig et al., 1992). However, the most prominent and widely studied effect of caffeine in the brain is its role as an antagonist of the inhibitory neurotransmitter, adenosine. Adenosine and some subtypes of its receptors, e.g. A_1 adenosine receptor, are found throughout the brain, and they reduce synaptic vesicle release in the presynaptic terminal among other functions (Fredholm et al., 1999; Goodman and Synder, 1982; Premont et al., 1979). Therefore, it is reasonable to hypothesize that blocking of the adenosine neurotransmission by caffeine may increase neural activity and whole-brain metabolic rate.

While conceptually simple, this question has not been thoroughly examined, mainly due to a scarcity of measurement techniques applicable in humans. Positron emission tomography (PET) has been used for the measurement of brain metabolism in clinical studies. However, there have been few reports on its use in studies of caffeine effect on the brain, possibly because of several factors such as concerns associated with repeated radiation exposure, the complexity in dynamic sampling of arterial blood, and the need of an onsite cyclotron in the case of oxygen metabolism measurement (Chen et al., 2009; Di et al., 2013; Park et al., 2014). Recently, we have developed a novel method that can provide a non-invasive (no exogenous tracer nor agent), rapid (<5 min), and reliable (coefficient of variation less than 4%) measurement of global cerebral metabolic rate of oxygen ($CMRO_2$) on a standard 3 T MRI (Liu et al., 2013; Xu et al., 2009, 2012). The present study applies this new method to examine the effect of caffeine ingestion on whole-brain oxygen metabolism in healthy humans.

Given that certain subtypes of the adenosine receptor, e.g. A_{2A}, are heterogeneously distributed in the brain (Fredholm et al., 1999; Mishina et al., 2007; Pelligrino et al., 2010), we further investigate

* Corresponding author at: Advanced Imaging Research Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA. Fax: +1 214 645 2744.
E-mail address: hanzhang.lu@gmail.com (H. Lu).

http://dx.doi.org/10.1016/j.neuroimage.2015.01.046
1053-8119/

regional differences in the brain's physiological response to caffeine. We measured cerebral blood flow (CBF) which reflects a combined contribution of a direct effect of caffeine on cerebrovasculature and an indirect effect through potential modulations on neural activity and brain metabolism (Alsop et al., 2014; Donahue et al., 2006; Kety and Schmidt, 1948). We reason that, if a regional heterogeneity can be identified, it would indicate that either the direct vasoconstriction effect is region-dependent or that neural response to caffeine is different across brain regions.

The present work therefore contains two sets of studies. In Study 1, we used a global $CMRO_2$ technique to examine dynamic changes in brain oxygen metabolism. Ten healthy human subjects took a 200 mg caffeine tablet and underwent a continuous MRI scan of 40 min, during which whole-brain $CMRO_2$ was measured every 4.5 min. Another ten subjects served as controls and underwent the same MRI session but did not take the caffeine tablet. In Study 2, ten healthy human subjects took a 200 mg caffeine tablet and underwent a continuous MRI scan of 40 min, during which voxel-by-voxel CBF maps were collected using arterial-spin-labeling (ASL) MRI.

Materials and methods

General

MRI scans were performed on a 3 T MRI system (Philips Healthcare, Best, The Netherlands). A body coil was used for radiofrequency transmission and a 32-channel head coil was used for receiving. Foam padding was used to stabilize the subject's head and to minimize motion. The study protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center. Each subject gave informed written consent before participating in the study. A total of thirty healthy subjects (27 ± 4 years old, 15 males, 15 females, 20 for Study 1 and 10 for Study 2) were recruited from the university campus through flyers. The participants were carefully screened and did not report neurological, psychiatric, endocrine disorders or diabetes according to self-completed questionnaires. The participants did not have MR contraindications such as metal implants, pacemaker, neurostimulator, body piercings, or claustrophobia. The participants were not regular coffee drinkers and were asked to avoid any type of caffeine beverages for a week before the experiment.

Study 1: the effect of caffeine ingestion on whole-brain $CMRO_2$

Experimental procedures

Ten subjects (28 ± 5 years old, range from 22 to 35, 5 males and 5 females) participated in the caffeine experiment. Fig. 1 illustrates the procedures at the research facility. The first time point of $CMRO_2$ measurement was obtained by 7.4 ± 0.3 (mean $\pm$ standard error) minutes after taking the tablet, which is considered a baseline value given the relatively small change in blood caffeine level at this early time point (Kamimori et al., 2002). We employed this procedure instead of the repositioning scheme (i.e. remove from and enter the scanner again) so that data fluctuation due to repositioning inconsistency is minimized and this allows us to perform continuous measurements without time gap. Arterial oxygen saturation (Y_a) was measured at finger with pulse oximetry (Invivo, Gainesville, FL).

Another ten subjects (27 ± 4 years old, range from 23 to 30, 6 males and 4 females) participated in the control experiment. The purpose of the control experiment was to test the possibility that the physiologic changes observed in the caffeine study were due to non-caffeine related effects such as drowsiness or fatigue caused by lying inside the scanner for 40 min. The procedures for the control experiment were identical to the caffeine ingestion experiment except that the participant did not take the caffeine tablet (Fig. 1).

Theory for the measurement of Global $CMRO_2$

Our approach to estimate $CMRO_2$ was based on the Fick principle (Jain et al., 2010; Kety and Schmidt, 1948; Rodgers et al., 2013; Xu et al., 2009), by which $CMRO_2$ can be calculated using:

$$CMRO_2 = CBF \cdot (Y_\alpha - Y_v) \cdot C_h \quad (1)$$

where $CMRO_2$ is in units of μmol/100 g/min, CBF is in units of ml/100 g/min, Y_a and Y_v (in percentage, %) are oxygenation in arterial and venous

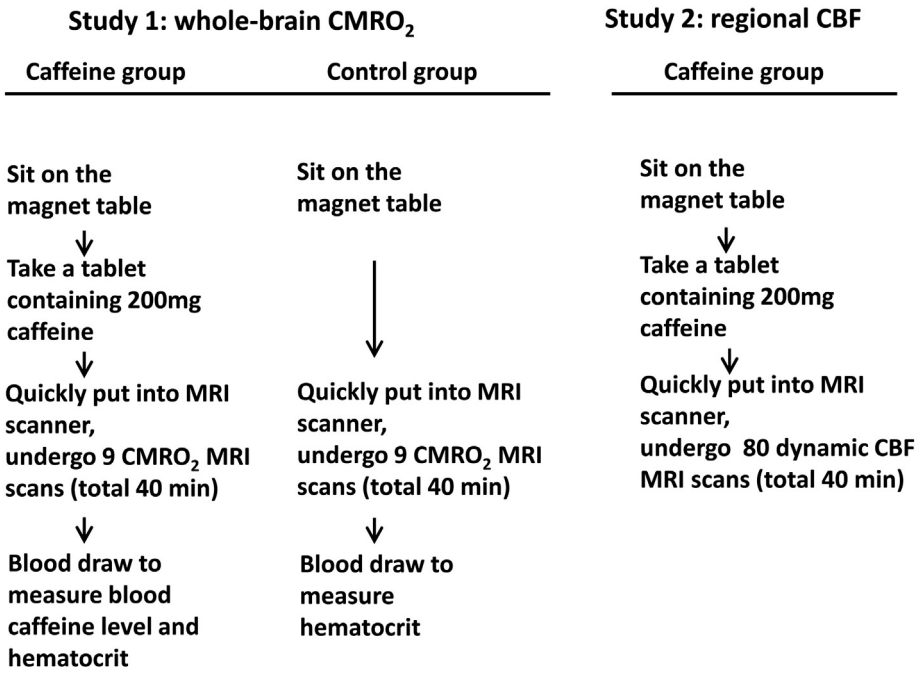

Fig. 1. Diagram of experimental procedures used in Study 1 and Study 2. Study 1 (left) contained a group of caffeine ingestion and a group of control participants. Study 2 (right) was performed on a caffeine ingestion group only as Study 1 already demonstrated that CBF does not change under the control condition.