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STIMULATION OF ARITHMETIC SKILLS AND HEMODYNAMIC EFFECTS BY COFFEE-DRINKING : DOUBLE-BLIND ANALYSIS WITH DIFFERENT CONCENTRATIONS OF CAFFEINE

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Abstract : Effects of caffeine on arithmetic performance were investigated with 217 university students. A double-blind study for arithmetic skill test and hemodynamic effects was carried out after drinking caffeine-free or caffeine-containing (100, 180 and 250 mg) coffee. Eleven rounds of the arithmetic tests were performed; first four rounds before, and subsequently seven rounds after coffee break. Each round consisted of three 1-min arithmetic tests. The arithmetic skill for each round was averaged. Simultaneously, heart rate and blood pressure once a round were also measured. The mean value of arithmetic skill at the 4th round (n=217) was 87.3±1.8/min. The heart rate and mean blood pressure were 72.7±1.7 beats/min and 101.7±4.1 mmHg. As compared with caffeine-free group, caffeine at 100 mg significantly enhanced arithmetic skill for 60 to 90 min after coffee-drinking. The mean blood pressure was increased for 30 to 60 min after coffee-drinking (with caffeine 180 mg). But the ratio of arithmetic errors and heart rate were unaffected. At 250 mg, caffeine rather depressed arithmetic skill and blood pressure. These results indicate that caffeine(100 to 180 mg)-containing coffee drinking can enhance arithmetic skill and modulate hemodynamic actions, presumably resulting from stimulation of the central nervous system and cardiovascular system.

Index Terms

caffeine, coffee, arithmetic skill, heart rate, blood pressure

INTRODUCTION

Caffeine (1, 3, 7-trimethylxanthine) contained in coffee, cocoa and tea has been taken for past 500 to 600 years and more, and is a widely used drug worldwide. Many epidemiologic studies of the public health consequences of caffeine intake have already been performed. In general, a cup of coffee contains approximately 120 mg of caffeine[10]. It is well known that caffeine stimulates the central nervous system, and also that too much coffee disturbs sleep and heart rhythms. Caffeine (75 to 100 mg) caused auditory and visual evoked responses[3,27], and increased reading speed and speech rate[4,14,26].

Application of caffeine affects the developed tension and the sinus rhythm in cardiac muscle. Satoh[18,19] and Satoh and Vassalle[20,21] have demonstrated that in canine Purkinje fibers and rabbit sino-atrial (SA) nodal cells, caffeine(0.5-10 mM)caused initially positive inotropic and chronotropic effects, and subsequently negative inotropic and chronotropic effects. The initial

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positive effect resulted from enhancement of the L-type Ca^{2+} current and Ca^{2+} release from sarcoplasmic reticulum (SR), due to accumulation of cAMP by phosphodiesterase (PDE) inhibition. The second negative effect was due to induction of cellular calcium overload by re-uptake blockade of Ca^{2+} into SR by caffeine itself. This is confirmed from the evidence that a dysrhythmia, due to a delayed and early afterdepolarization or a transient inward current and an inward tail current, occurred under the depressant condition[6,18,19,22].

We have already shown the efficiency of caffeine for arithmetic skill[23]. The aim of the present study is to examine by a double blind method whether or not a change in arithmetic skill is produced after coffee-drinking (caffeine-free or caffeine-containing) and especially which concentrations are effective, by using different concentrations of caffeine(100 to 250 mg). Also, we sought to examine the effects on heart rate (HR) and blood pressure (BP).

MATERIALS AND METHODS

Measurement of arithmetic performance

The arithmetic skill test of 217 university students was investigated, according to the methods developed by Sakuma[17]. A double-blind study was carried out, in which caffeine-free or caffeine-containing (100, 180 or 250 mg) coffee was taken immediately after the 4th round test. Each round consisted of three one-minute arithmetic tests every 15 min, as shown in Fig. 1. An arithmetic test was conducted for 1 min. The arithmetic skill test was simply an addition using an Uchida-Kraepelin's test (Japan Psychotech. Inc. Co.). The average value of the three arithmetic tests in a round was represented. The first (−45 min) to fourth (0 min) round tests were carried out to become skilled in the arithmetic test. The average value at the 4th round test was taken as a control value. After coffee-drinking, the arithmetic tests were repeated 7 rounds more every 15 min. The significance of differences was assessed with ANOVA and Student's t-test for paired data. Values are presented as mean±S. E. M.

Measurements of heart rate and blood pressure

Heart rate (HR) and blood pressure (BP) were measured once a round after three arithmetic

PROCEDURE

• −45 min	1 st	Kraepelin Test
• −30 min	2 nd	Kraepelin Test
• −15 min	3 rd	Kraepelin Test
• 0 min	4 th	Kraepelin Test

Coffee Break
Caffeine-free Ceffee or
Caffeine (100 mg. 180 or 250 mg)
-containing Coffee

• 15 min	5th	Kraepelin Test
• 30 min	6 th	Kraepelin Test
• 45 min	7 th	Kraepelin Test
• 60 min	8 th	Kraepelin Test
• 75 min	9 th	Kraepelin Test
• 90 min	10 th	Kraepelin Test
• 115 min	11 th	Kraepelin Test

Fig. 1. Procedure of Kraepelin tests. The tests were carried out four times (−45 to 0 min) before, and seven times (15 to 115 min) after coffee-drinking. One round of test was composed of three times-Kraepelin tests for 1 min.

skill tests. The BP was calculated [diastolic pressure+(systolic pressure−diastolic pressure)×1/3] and was indicated as a mean BP.

Coffee making

Caffeine-free instant coffee (Nescafe Red Label, Nestle Co., Tokyo) was used. A cup of coffee (150-200 ml) was regularly made with a full spoon of the coffee, one of sugar and one of creaming powder (Creama, Yukijirushi Co., Tokyo). In the caffeine-containing coffee, caffeine (100, 180 or 250 mg) was added to approximately three fourth of 217 cups at random.

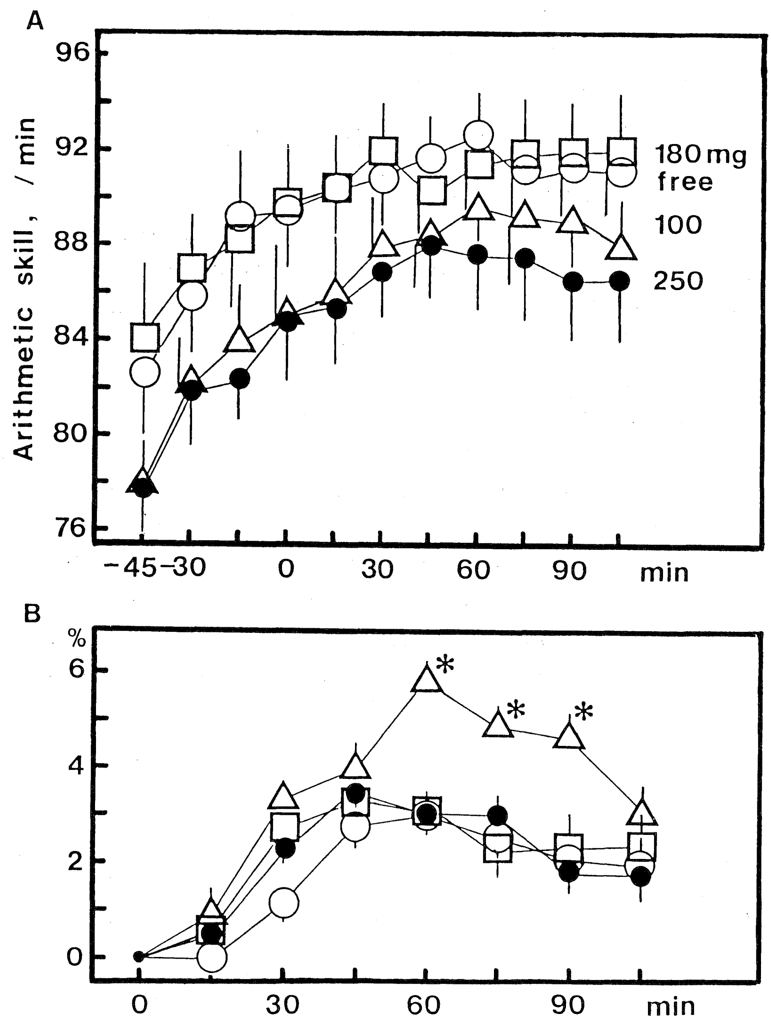

Fig. 2. Effect of caffeine on arithmetic skill before and after coffee-drinking. **A**: Time-dependent changes in the arithmetic skill at different caffeine concentrations. The averaged scores for three times-Kraepelin tests (one round) are plotted. **B**: Normalized curves in caffeine-free and caffeine-containing groups, taking fourth test (0 min) as a base. Symbols used are caffeine-free (open circles, n=55), 100 mg (triangles, n=56), 180 mg (squares, n=54), and 250 mg (filled circles, n=52) of caffeine. Values are represented as mean±S. E. M. *: $P<0.05$, with respect to control values.

The cups were numbered by a controller, and it was impossible for the subjects to distinguish between caffeine-containing or caffeine-free coffee, or to estimate the concentrations of caffeine.

RESULTS

Effects on arithmetic skill

The arithmetic skill test was examined before and after drinking caffeine-free coffee for 55 students and caffeine-containing coffee for 162 students. Figure 2A shows the time-dependent changes in arithmetic skill in the caffeine-free group (55 students) and in three caffeine-containing groups (56 students at 100 mg, 54 students at 180 mg and 52 students at 250 mg). At -45 to 0 min before coffee-drinking, arithmetic skills in all the groups were increased round by round. The average value of all the students (n=217) was 87.3 ± 1.8 per min. The values are normalized by taking those at the 4th round as 100 % (Fig. 2B). After coffee-drinking, the skills both in caffeine-containing groups and even in the caffeine-free group were also increased further by about 3-4% at 15 to 45 min. Just at 100 mg (n=56), the skill was significantly enhanced. The enhancement lasted for 1.5 hr after coffee-drinking ; by 5.8 ± 0.3 % ($P < 0.05$) at 60 min, by 5.0 ± 0.5 % ($P < 0.05$) at 75 min, and by 4.7 ± 0.5 % ($P < 0.05$) at 90 min after

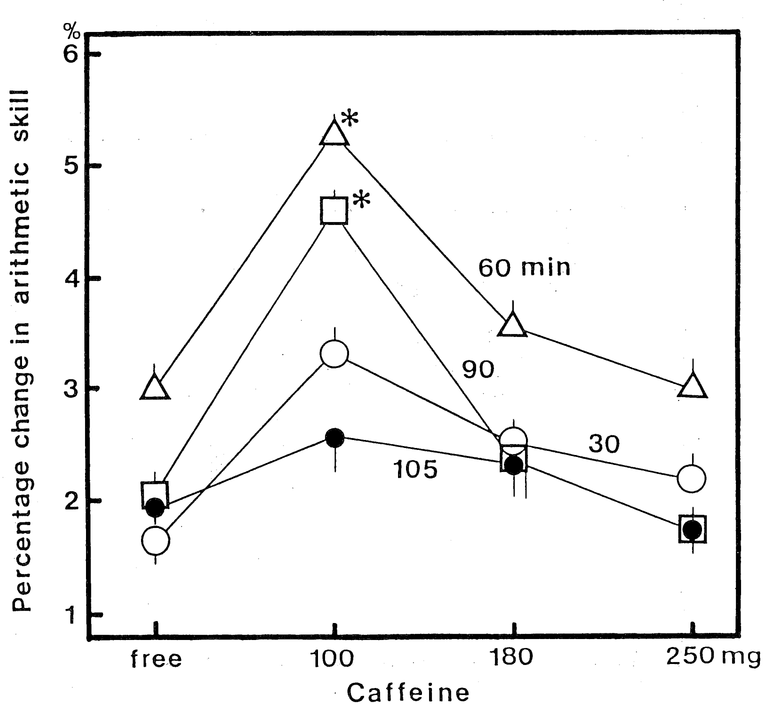

Fig. 3. Concentration-response curves for the arithmetic skill at different caffeine concentrations. The average scores for one round are plotted. Number of values was free (n=55), 100 mg (n=56), 180 mg (n=54), and 250 mg (n=52). Symbols used are 30 min (open circles), 60 min (triangles), 90 min (squares), and 105 min (filled circles) after coffee-drinking. Values are represented as mean±S. E. M. * : $P < 0.05$, with respect to control values.

coffee-drinking, as compared with the values in the caffeine-free group (n=55). Caffeine at 180 and 250 mg rather depressed arithmetic skill. Three of 56 students in the 250 mg caffeine group complained of slight nausea.

Figure 3 shows the concentration-response curves at different times after coffee-drinking. The percentage values were plotted by taking the value at the fourth round in each group as a control. Significant effective responses were observed only 60 and 90 min after coffee

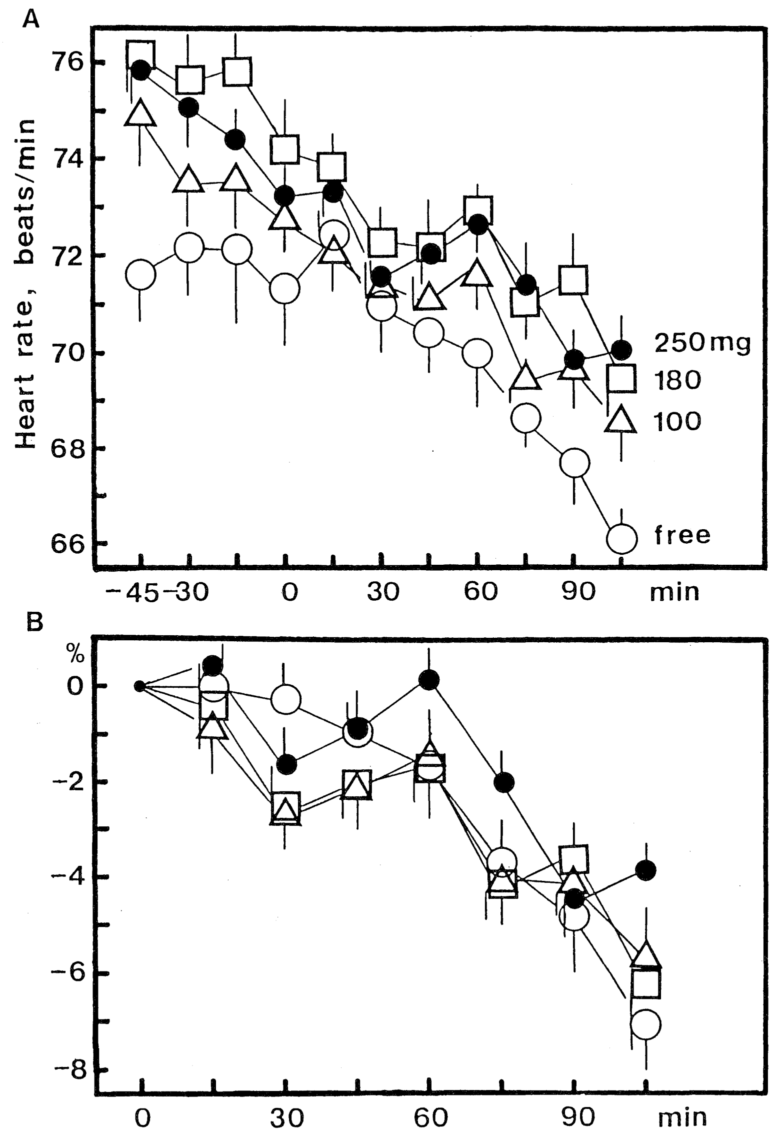

Fig. 4. Effect of caffeine on heart rate before and after coffee-drinking. **A**: Time-dependent changes in the heart rate at different caffeine concentrations. **B**: Normalized curves in caffeine-free and caffeine-containing groups, taking the fourth test (0 min) as a base. Symbols used are caffeine-free (open circles, n=55), 100 mg (triangles, n=56), 180 mg (squares, n=54), and 250 mg (filled circles. n=52) of caffeine. Values are represented as mean±S. E. M.

containing 100 mg caffeine ($n=56$, $P<0.05$).

In the arithmetic errors, the mean ratio at the 4th round in 217 students was 0.25 ± 0.02 % (ranging from 0 to 3.75 %). The ratio was decreased in all the groups round by round. But the difference in each group was not statistically significant.

Effect on heart rate

The heart rate (HR) was decreased time-dependently, before and after coffee-drinking and independent of coffee-drinking with and without caffeine (Fig. 4A). The HR reached an almost steady state at the 4th round, and the average value was 72.7 ± 1.7 beats/min ($n=217$).

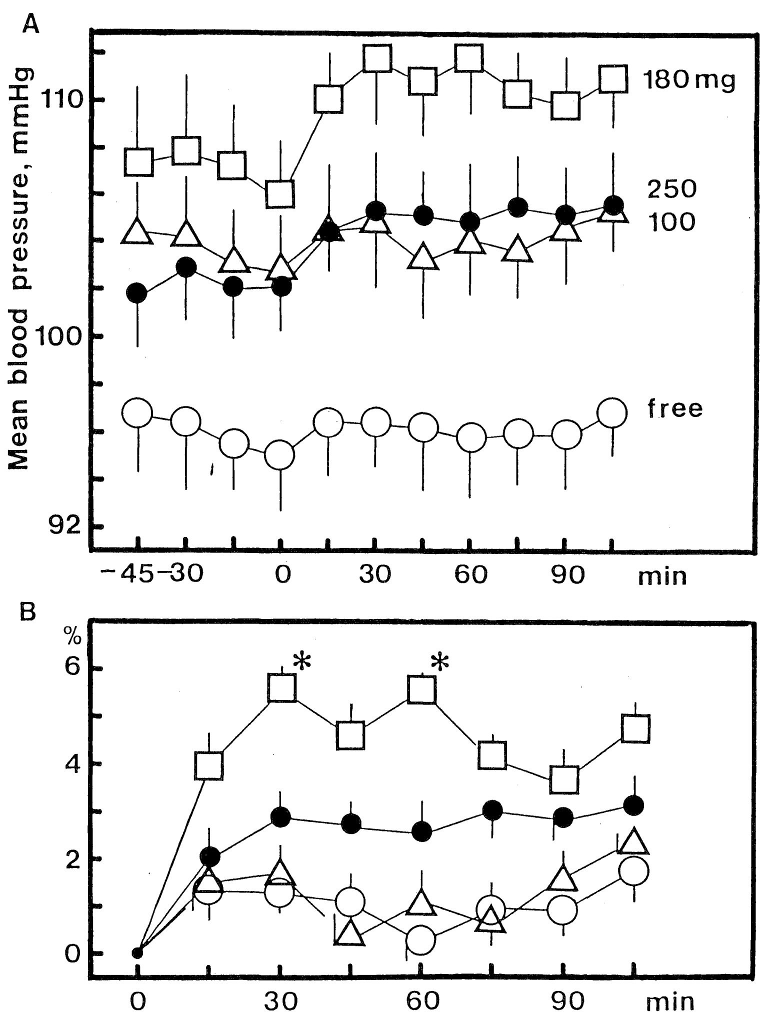

Fig. 5. Effect of caffeine on blood pressure before and after ceffee-drinking. **A**: Time-dependent changes in the mean blood pressure at different caffeine concentrations. **B**: Normalized curves in caffeine-free and caffeine-containing groups, taking the fourth test (0 min) as a base. Symbols used are caffeine-free (open circles, $n=55$), 100 mg (triangles, $n=56$), 180 mg (squares, $n=54$), and 250 mg (filled circles, $n=52$) of caffeine. Values are represented as mean±S. E. M. * : $P<0.05$, with respect to control values.

After drinking coffee, however, the HR was decreased further in all groups. Figure 4B shows the normalized curves. The difference among the groups after coffee-drinking was not significant.

Effects on mean blood pressure

Blood pressure (BP) also decreased for three tests before coffee-drinking (−45, −30 and −15 min) (Fig. 5A). The average value was 101.7±4.1 mmHg (n=217). As shown in Fig. 5B, the normalized time-dependent curves represent an increase in the mean BP at 180 mg caffeine after coffee break. The value (n=54) was 5.56±0.3 % ($P<0.05$) at 30 min, and 5.54±0.2 % ($P<0.05$) at 60 min. At 250 mg, caffeine increased the BP, but not to a significant extent (by 2.0 to 3.2 %, n=52). Figure 6 shows the concentration-response curves at different times after coffee-drinking. At 180 mg caffeine, the BP was increased 30 and 60 min after coffee-drinking.

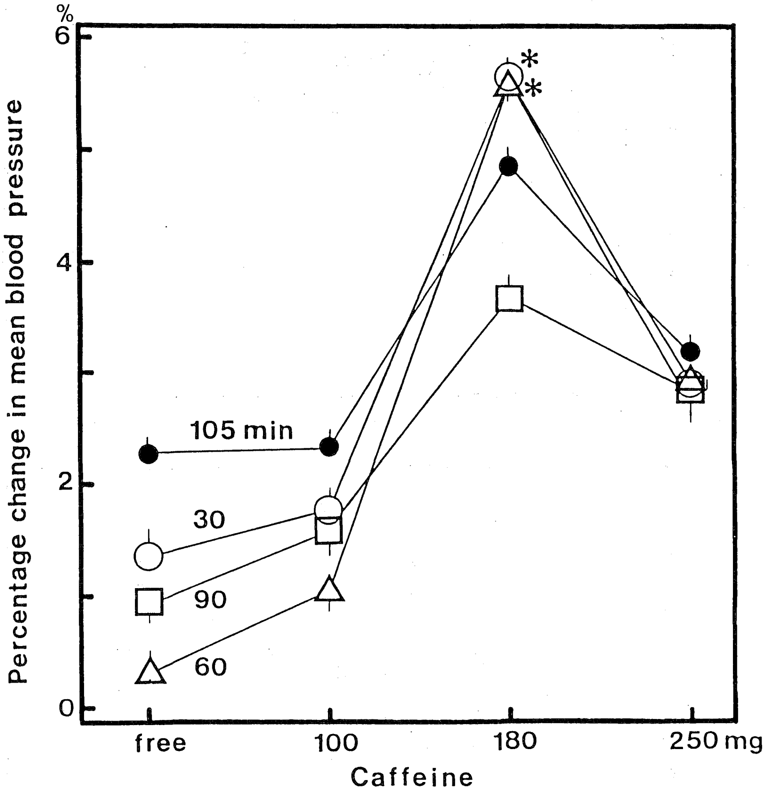

Fig. 6. Concentration-response curves for mean blood pressure at different times before and after coffee-drinking. Symbols used are 30 min (open circles), 60 min (triangles), 90 min (squares), and 105 min (filled circles) after coffee drinking. Number of values was free (n=55), 100 mg (n=56), 180 mg (n=54), and 250 mg (n=52). Values are represented as mean±S. E. M. ∗ : $P<0.05$, with respect to control values.

DISCUSSION

Caffeine is a pharmacologically active chemical, which as coffee or tea has been in wide-spread use for a long time. The present experiments by means of the double-blind study of 217 university students showed that caffeine (after coffee-drinking) enhanced arithmetic skill at 100 mg and increased the mean blood pressure at 180 mg. Caffeine is water-soluble, and is completely absorbed from caffeinated beverages. The caffeine concentration reaches a peak in the blood at 30-60 min later[1]. The half-life ($T_{1/2}$) is 4-6 hr. These pharmacological characteristics are reflected in the data of the present studies. The significant differences for arithmetic skill and the BP were observed 30 to 90 min after coffee-drinking.

Arithmetic skill

In general, caffeine at relatively higher concentrations increases sleep latency and decreases total sleep time. It has also been known that caffeine is primarily a stimulant, increasing the flow of thought and vigilance, reducing fatigue, and shortening motor reaction time[11,24]. In the present experiments, arithmetic skills in all the groups (with and without caffeine) were increased round by round, irrespective of coffee-drinking, consistent with our previous report[23]. The increase would probably be due to habituation and learning by the repeated tests, as would be the decrease in arithmetic errors (but not significant). Caffeine just at 100 mg enhanced the arithmetic skill significantly. This would be due to a stimulatory action on the central nervous system. Furthermore, the accumulation of cAMP by its phosphodiesterase (PDE) inhibitory action would cause vasodilation in brain and other tissues. The vasodilation might indirectly contribute to the elevation of the brain activity.

Benowitz[1] has reported that alcohol inhibits caffeine metabolism, whereas tobacco smoke accelerates it. In this experiment, smokers were about 25 % of all students. But they did not smoke during the tests for about 3 hrs (11 rounds every 15 min). Thus, it seems unlikely that the caffeine actions were modified by smoking, although it is possible that nicotine level in blood by smoking before the start of the tests might be kept relatively high. Arithmetic skill and HR were significantly affected at 30 and 90 min later. The effective duration of caffeine was not different from the previous report[23].

The response to caffeine is dependent on the sensitivity of individuals. The importance of tolerance or adaptation to the caffeine actions must be considered. It has been reported that when even one or two cups of coffee are consumed during a day, a tolerance develops to the caffeine actions within a few days[16]. The tolerance is associated with an increased number of adenosine receptors in the brain[2,5]. Adenosine is a competitive antagonist of caffeine. In this study, however, it seems unlikely that the caffeine actions are strongly influenced by a developed tolerance. Caffeine produced significant actions, although most students (about 80 %) usually had one or several cups of coffee a day. The enhancement of arithmetic skill was consistent with the results of Sakuma[17] and Horiuchi et al.[8]. Therefore, we conclude that caffeine (about 120 mg) in a cup of coffee can enhance arithmetic skill.

Hemodynamic effects

In the present study, the HR in all the groups decreased round by round even before coffee-drinking (but not significantly). This is consistent with our previous report[23], probably due to the subjects becoming relaxed mentally. After coffee-drinking, the HR decrease was elicited further. This would be induced via baroreceptor-mediated reflexes. The decrease might have resulted from refreshment (coffee-break) by driking a cup of coffee. On the other hand, a significant increase in the BP only at 180 mg caffeine occurred at 30 to 60 min later. The amount of caffeine is equivalent to approximately two cups of coffee. It has been shown that caffeine (two cups of coffee) increases blood pressure (by 5-10 mmHg), decreases HR slightly, and causes systemic release of epinephrine, norepinephrine and renin[12,15]. The pressor effect might be due to an increase in cardiac output (via the PDE inhibition by caffeine) and peripheral vasoconstriction (via the adenosine antagonism).

Caffeine exerts multiple influences on different tissues. Application of caffeine causes relaxation of smooth muscle, stimulation of skeletal muscle, and diuretic action[13]. Satoh and colleague have already shown that in isolated cardiac muscles, caffeine (0.5-10 mM) caused the positive inotropic and chronotropic effects, and subsequently the negative inotropic and chronotropic effects[18,19,20,21]. As a result, caffeine induced cellular calcium overload. Then, a dysrhythmia occurred : delayed and/or early afterdepolarizations[6,18,19,22]. Clinical reports reflected the present results. Mean plasma caffeine concentration in 600 medical outpatients was 2.1 mg/l (ranging from 0.2 to 13.1 mg/l)[25]. We have no information about how much the concentration of caffeine is elevated by a cup of coffee (120 mg caffeine) ; this must be examined in future extensive studies. The elevation of plasma content of caffeine in heavy coffee drinkers may induce calcium overload. For one or two cups of coffee a day, the relative risk is 1.3, and for over five cups per day, is 2.5, as compared with no coffee-drinking[9,28]. In clinical use, caffeine as a drug is applied to patients with headache and postprandial orthostatic hypotension[7].

CONCLUSION

Caffeine produces significant actions on arithmetic skill at 100 mg and the BP at 180 mg for university students. These results strongly indicate the beneficial effect of several cups of coffee on work performance. Although caffeine gives us so many benefits, it may also bring dangerous risks. Heavy coffee-drinkers need to be careful for their health, and especially for aggravating effects on cardiac diseases.

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