ENHANCEMENT OF ARITHMETIC SKILLS BY COFFEE-DRINKING : DOUBLE-BLIND STUDY FOR CAFFEINE-CONTAINING AND CAFFEINE-FREE COFFEES

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Summary : Effects of caffeine on arithmetic performance were investigated with 99 university students. A double-blind study for arithmetic skill test was carried out, after drinking caffeine-free or caffeine-containing (180 mg) coffee. Eight rounds for the arithmetic tests were performed; four rounds before, and four rounds after coffee break. Each round was 1-min arithmetic tests three times with 1-min intervals. The arithmetic skill and the ratio of arithmetic errors per each round were averaged. Simultaneously, heart rate was also measured. The mean values of arithmetic skill and the ratio of errors at the 4 th round (n=99) were 81.4±1.7/min and 0.28±0.02 %. The heart rate was 76.9 ± 1.5 beats/min. Before and after coffee-drinking, arithmetic skill was enhanced, whereas the heart rate was significantly decreased. As compared with the caffeine-free group, caffeine significantly enhanced the arithmetic skill 45 and 60 min after coffee-drinking. But the ratio of arithmetic errors was not affected. The heart rate was significantly decreased only at 45 min later. These results indicate that caffeine (-containing coffee drinking) can enhance arithmetic skill and decrease the heart rate, presumably resulting from stimulation of the central nervous system.

Index Terms

caffeine, coffee, double-blind study, arithmetic performance, heart rate

INTRODUCTION

Caffeine (1, 3, 7-trimethylxanthine) is probably the most widely used drug worldwide, containing in a coffee, cocoa and tea. There have been many epidemiologic studies of the public health consequences of caffeine intake. Mean caffeine content per drink is 70 mg for instant coffee, 120 mg for brewed coffee, and 50 mg for black tea[1]. It is well known that too much coffee disturbs sleep and heart rhythms. Also, a withdrawal syndrome of lethargy, irritability, and headache, has been recognized by coffee-drinking (over about six cups)[2].

Caffeine regulates contractility in cardiac muscle. In isolated cardiac muscle, caffeine (0.5 -10 mM) caused initially positive inotropic and chronotropic effects, and subsequently negative inotropic and chronotropic effects[3][4]. The initial positive effect was due to Ca^{2+} release from sarcoplasmic reticulum (SR), accumulation of cAMP by phosphodiesterase (PDE) inhibition, and enhancement of the Ca^{2+} current. The negative effect was due to induction of cellular calcium overload by uptake blockade of Ca^{2+} into SR. Because a dysrhythmia, due to delayed and early afterdepolarizations (or a transient inward current (I_{Ti}) and an inward tail current

(I_{ex})), occurred under the depressant condition[5)6)7)]. In addition, it has already been reported that caffeine causes dilation of smooth muscle, stimulation of skeletal musle, and diuretic action[8)].

Thus, caffeine possesses multiple actions on different tissues. The aim of the present study is to examine whether or not a change in the arithmetic skill is produced, for 1 hr after coffee-drinking ; caffeine-free or caffeine-containing. Also, we sought to examine the effect on heart rate (HR).

MATERIALS AND METHODS

Measurement of arithmetic performance

The arithmetic skill test was investigated with 99 university students, according to the methods developed by Sakuma[9)]. Double-blind study was carried out, in which caffeine-free or caffeine-containing (180 mg) coffee was taken immediately after the 4 th round test. Each round was composed of 1-min arithmetic test three times with 1-min intervals. The average value of the three arithmetic tests in a round was calculated. The arithmetic skill test was simply an addition using an Uchida-Kraepelin's test (Japan Psychotech. Inc. Co.). The first (−45 min) to fourth (0 min) round tests were carried out to become skillful in the arithmetic test. The averaged value at the 4 th round test was taken as a control value. After coffee-drinking, the arithmetic tests were repeated 4 rounds more every 15 min. The significance of differences was assessed with Student's t-test for paired data. Results are presented as mean ±S. E. M.

Measurement of heart rate

Heart rate (HR) was measured once a round 1 min after three arithmetic skill tests. The

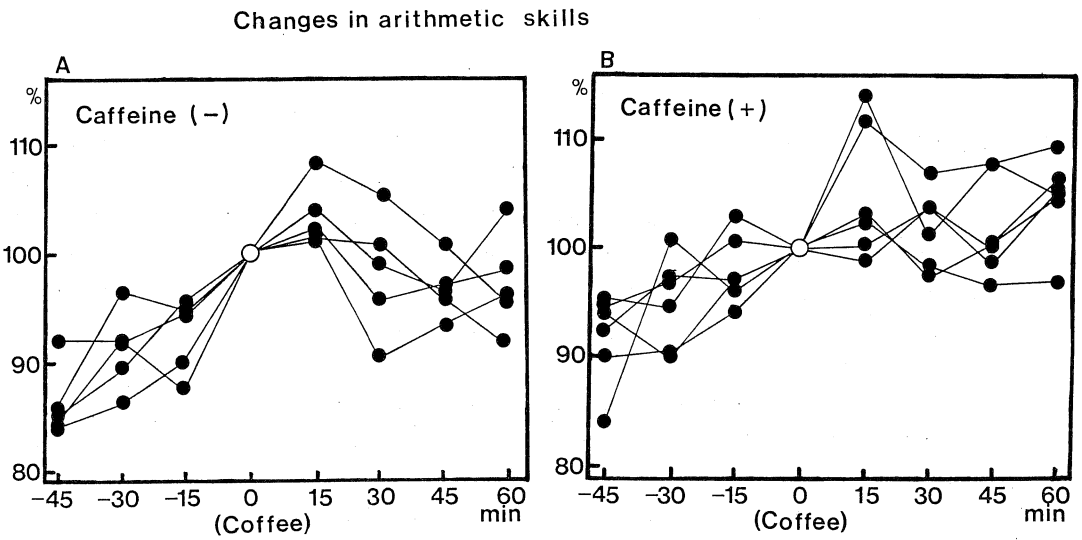

Fig. 1. Time-dependent changes in arithmetic skills of individuals before and after coffee-drinking. Coffee was drunken after an arithmetic skill test of 4th round. The values are normalized by taking those at 4th round as 100 %. A : caffeine-free coffee (n=5). B : Caffeine-containing coffee (n=6).

value was counted for 30 sec, and was doubled.

Coffee making

Caffeine-free instant coffee (Nescafe red-label, Nestle Co.) 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.). In the caffeine-containing coffee, caffeine (180 mg) was added approximately half of 99 cups at random. The cups were numbered by a controller, and it was impossible to distinguish between caffeine-containing or caffeine-free coffee.

RESULTS

Time-dependent effects on arithmetic skill and heart rate

The arithmetic skill test was examined before and after drinking caffeine-free coffee for 48 students and caffeine-containing coffee for 50 students. Figure 1 A and B, as an example of an individual case, shows the time-dependent percentage changes in the arithmetic skill in the caffeine-free group (5 students) and in the caffeine-containing group (6 students). The values are normalized by taking those at the 4 th round as 100%. At 45 to 0 min before coffee-drinking, the arithmetic skills in both groups were increased round by round. After coffee, the skills were also increased further by $4.9 \pm 0.7\%$ at 15 min, by $1.9 \pm 0.5\%$ at 30 min, by $2.0 \pm 0.5\%$ at 45 min, and by $4.6 \pm 0.6\%$ at 60 min in the caffeine-containing group ($n = 6$), and in the caffeine-free group ($n = 5$), were increased by $3.4 \pm 0.3\%$ at 15 min and rather decreased by $1.9 \pm 0.6\%$ at 30 min, by $3.4 \pm 0.4\%$ at 45 min, and by $2.9 \pm 0.6\%$ at 60 min. Arithmetic skill at the 4 th round for all students ($n = 99$) is shown in histogram (Fig. 2). The average value was 81.4 ± 1.7/min (ranging from 45 to 115/min). In ratio of arithmetic errors at the 4 th round, no error occurred in 55 students (Fig. 3). The mean ratio was $0.28 \pm 0.02\%$ ($n = 99$) (ranging from 0 to 3.89%). Similarly, the histogram for HR at the 4 th round is shown in

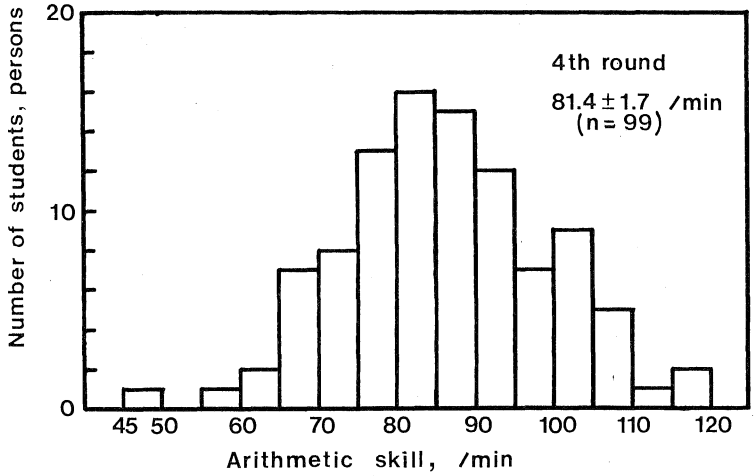

Fig. 2. Histogram of arithmetic skills in ninety-nine students. The values are obtained only at 4th round (as control).

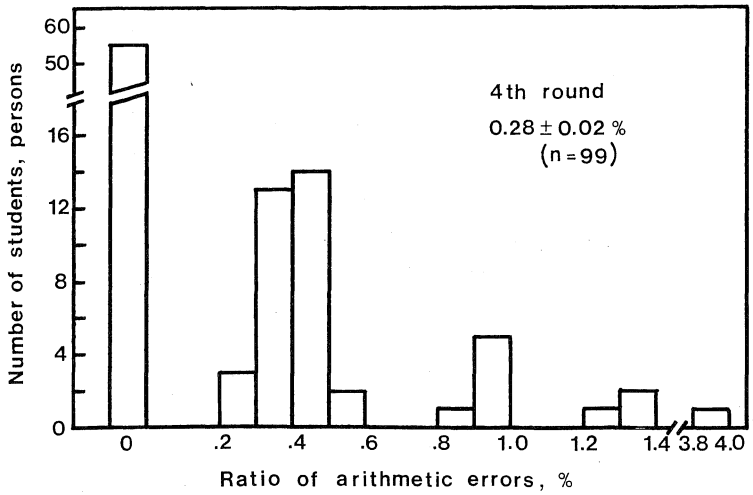

Fig. 3. Histogram for ratio of arithmetic errors at 4th round in all students.

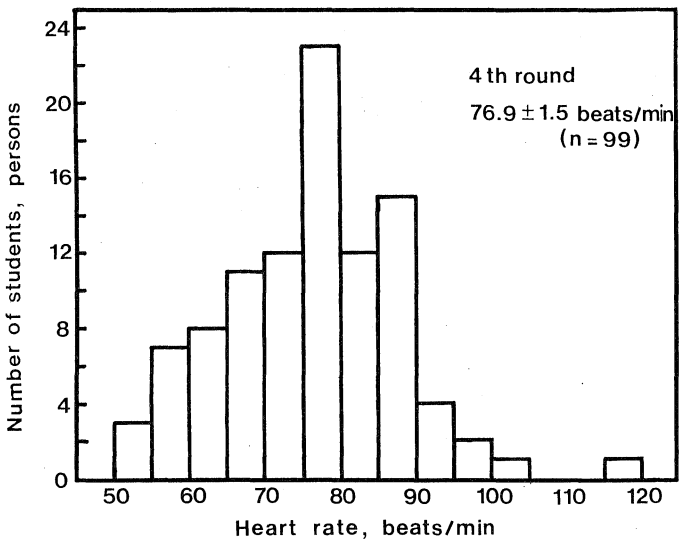

Fig. 4. Histogram of heart rate of all students at 4th round before coffee-drinking.

Fig. 4. The values ranged from 52 to 118 beats/min. The mean value was 76.9 ± 1.5 beats/min (n = 99). Surprisingly, the HR of only one student was 118 beats/min even at the 4 th round (45 min after starting the tests). This student ranged from 110 to 124 beats/min during the tests.

Effect of caffeine on arithmetic skill

Effects of caffeine (180 mg) on arithmetic skill were examined, and were compared between the caffeine-free (n = 48) and caffeine-containing groups (n = 48). The mean values in both

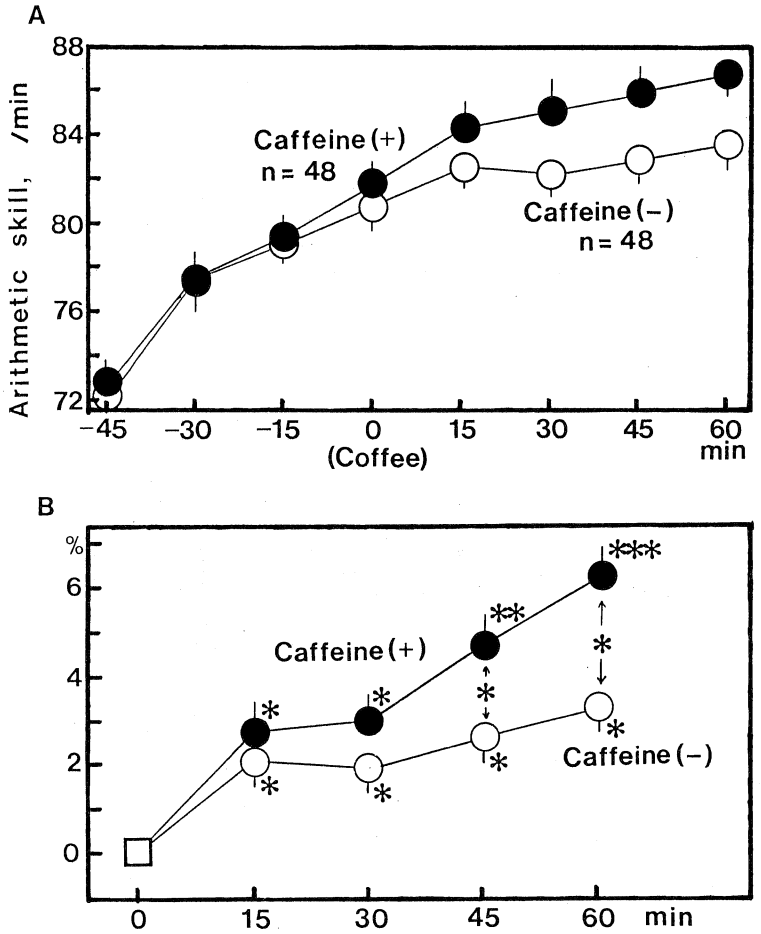

Fig. 5. Effect of caffeine on arithmetic skill after coffee-drinking. A : Time -dependent changes in the skill. The averaged number which students calculated for one min are plotted. B : Normalized curves in caffeine -free and caffeine-containing groups. Values are represented as mean±S. E. M. in caffeine-free (open circles) and in caffeine-containing (filled circles). *: $P<0.05$, **: $P<0.01$, ***: $P<0.001$, with respect to control values.

groups are plotted in Fig. 5 A. Before coffee-drinking, there was almost less difference, but the values at 45 and 60 min after the coffee were significantly increased in the caffeine-containing group more than in the caffeine-free group (Fig. 5 B). The curves are normalized by taking the values at the 4 th round as control. The mean values in the caffeine-free and caffeine-containing groups were $2.6 \pm 0.5\%$ and $4.8 \pm 0.5\%$ at 45 min ($P<0.05$), and $3.3 \pm 0.6\%$ and $6.2 \pm 0.6\%$ at 60 min ($P<0.05$). The enhancement in both groups lasted for 1 hr after coffee -drinking.

The differences of arithmetic skills, between the values at the 7 th and 4 th rounds and between the values at the 8 th and 4 th round, were also analyzed (Fig. 6 A and B). The mean

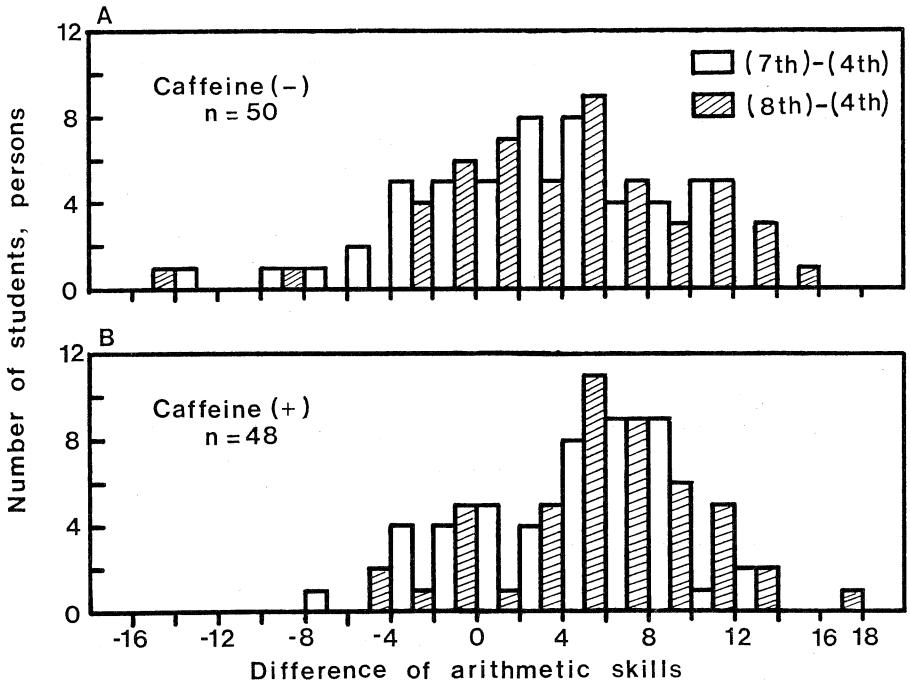

Fig. 6. Histogram for differences of arithmetic skills. The differences were taken from values at 7th round to those at 4th round (open columns), and from the values at 8th round to those at 4th round (shadow columns). A: Caffeine-free group (n=50). B: Caffeine-containing group (n=48).

values in the caffeine-free and caffeine-containing groups were 2.2 ± 0.5/min and 4.0 ± 0.6/min at the 7 th minus 4 th round, and more 3.2±0.5/min and 5.0±0.5/min at the 8 th minus 4 th round, respectively.

The ratio of arithmetic errors was decreased in both groups round by round (Fig. 7 A). The difference was not statistically significant (Fig. 7 B).

Effect of caffeine on heart rate

The HR was decreased time-dependently, before and after coffee-drinking (Fig. 8 A). The HR reached an almost steady state at the 4 th round ; 77.7 ± 1.7 beats/min (n = 48) in the caffeine-containing group and 76.0 ± 1.5 beats/min (n = 48) in the caffeine-free group. After drinking coffee, however, HRs were decreased further in both groups. Figure 8 B shows the normalized curves. The difference between both groups was statistically significant only at 45 min after coffee-drinking ($P<0.05$).

DISCUSSION

The results in this double-blind study of 99 university students show that caffeine enhanced arithmetic skill and decreased HR. Coffee and tea (containing caffeine) are in widespread use. Caffeine is one of the consumed pharmacologically active chemicals. Caffeine is completely

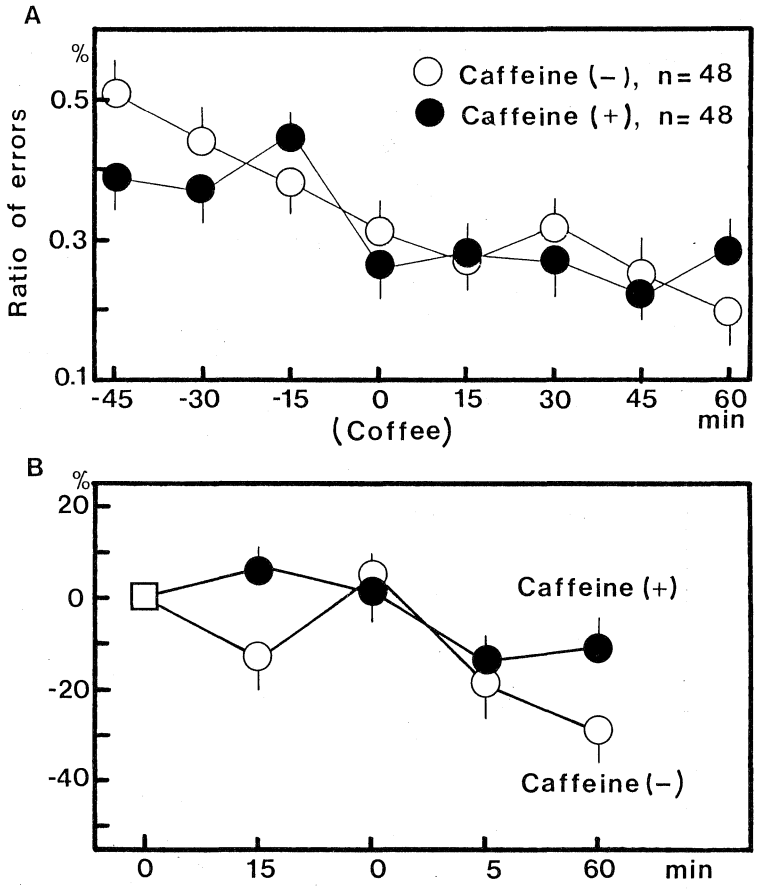

Fig. 7. Change in the ratio of arithmetic errors. A: Ratio of erros. B: Normalized the percentage change in the ratio of errors. Values are represented as mean±S. E. M. in caffeine-free group (open circles) and in caffeine-containing group (filled circles).

absorbed from caffeinated beverages, and reaches a peak in the blood at 30-60 min later[2]. The half-life ($T_{1/2}$) is 4-6 hr. This is consistent with the present results, in which the significant differences for arithmetic skill and HR were observed 45 to 60 min after coffee-drinking. Interestingly, caffeine enhanced arithmetic skill and decreased HR. The caffeine-induced effects are discussed below.

Effects on central nervous system

It is well-known that caffeine at relatively higher concentrations may increase sleep latency and decrease total sleep time. In addition, caffeine is primarily a stimulant, increasing flow of thought and vigilance, reducing fatigue, and decreasing motor reaction time[10)11)]. In the present experiments, arithmetic skills in both groups were increased round by round, before and after coffee-drinking. The increase would be due to habituation and learning by the repeated tests, as would the decrease in arithmetic errors (but not significant). Furthermore, caffeine actually

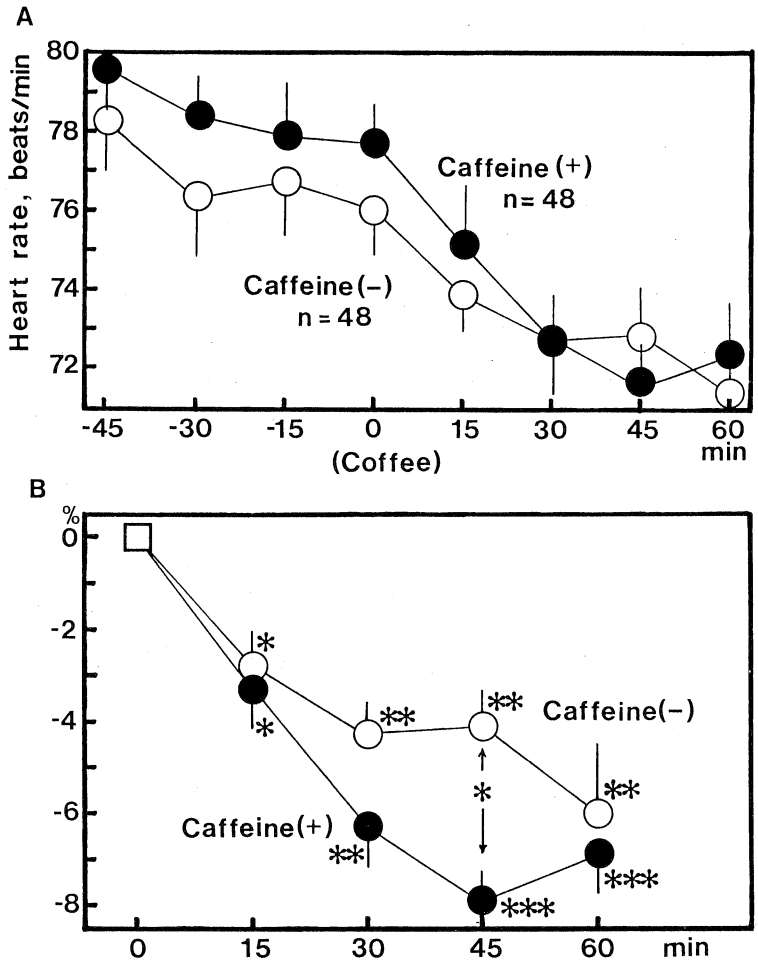

Fig. 8. Time-dependent change in heart rate before and after coffee-drinking. A : Heart rates in caffeine-free and in caffeine-containing groups. B : Normalized curves for change in heart rate. Values are represented as mean±S. E. M. in caffeine-free group (open circles) and in caffeine-containing group (filled circles). *: $P<0.05$, **: $P<0.01$, ***:$P<0.01$, with respect to control values.

enhanced arithmetic skill significantly. This would be due to a stimulatory action on the central nervous system. Caffeine also possesses PDE inhibitory action. The resultant accumulation of cAMP would cause vasodilation in brain and other tissues. The vasodilation might indirectly elevate the brain activity.

Alcohol inhibits caffeine metabolism, whereas tobacco smoke accelerates it[2]. In this experiment, smokers were about 26% of all students ; 9 students in the caffeine-free group and 17 students in the caffeine-containing group. It seems unlikely that the caffeine actions were affected by smoking, because arithmetic skill and HR were significantly modified at 45 and 60 min later. During the tests for about 3 hrs (every 15 min in 8 rounds), the smokers might not

have enough time to smoke.

The effects induced by caffeine would be dependent on the sensitivity of individuals. The importance of tolerance or adaptation to the caffeine actions must be considered. When caffeine is consumed throughout the day (one or two cups of coffee), tolerance develops to many of the caffeine actions within a few days[12]. The tolerance is associated with an increased number of adenosine receptors in the brain[13][14]. Adenosine actions are antagonized by caffeine. In this study, however, it seems unlikely that the caffeine actions would be affected by a developed tolerance, because caffeine produced the significant actions. In addition, the enhancement of arithmetic skill was consistent with the results of Sakuma[9] and Horiuchi et al.[15]. Therefore, we concluded that caffeine (a cup of coffee) can enhance arithmetic skill.

Cardiovascular effects

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[16][17]. The pressor effect might be due to an increase in cardiac output (via PDE inhibition) and peripheral vasoconstruction (via adenosine antagonism). The decrease in HR would be induced via baroreceptor-mediated reflexes. In the present study, the decrease in HR in both groups was elicited round by round even before coffee-drinking, probably due to the subjects becoming relaxed mentally. After coffee-drinking, HR in both groups was significantly decreased. The decrease might have resulted from refreshment (coffee-break) by drinking a cup of coffee after the 4 th round. And actually, a significant decrease in HR between both groups occurred only at 45 min later. The significance at only one point might be due to the small number of subjects and caffeine tolerance (which appears to have contributed less).

In isolated cardiac mucles, caffeine (0.5-10 mM) caused positive inotropic and chronotropic effects, and subsequently negative inotropic and chronotropic effects[3][4]. Finally, caffeine induced cellular calcium overload. As a result, a dysrhythmia occurred; delayed and/or early afterdepolarizations[5][6][7]. These results are reflected in clinical reports. In 600 medical outpatients, mean plasma caffeine concentration was 2.1 mg/l (ranging from 0.2 to 13.1 mg/l)[18]. The plasma content of caffeine may induce calcium overload, although the incidence would be modulated by individual sensitivity. The relative risk is 1.3 for one or two cups of coffee per day, and 2.5 for more than five cups per day, as compared with no coffee-drinking[19][20]. But clinically, caffeine is applied to patients with postprandial orthostatic hypotension[21]. Thus, caffeine gives us so many benefits, but also has dangerous risks.

Conclusion

Caffeine possesses significant actions on arithmetic skill and HR of university students. These results may strongly suggest the beneficial effect of several cups of coffee when the students study for examinations. In the future, when the arithmetic test will be carried out,we also want to measure blood pressure simultaneously as well as HR. Furthermore, we could manage the lives of individuals, such as their caffeine intake and smoking through a whole day.

References

1) **Lelo, A., Miners, J. O., Robson, R.** and **Birkett, D. J.** : Assessment of caffeine exposure : Caffeine content of beverages, caffeine intake, and plasma concentrations of methylxanthines. Clin. Pharmacol. Ther. **39** : 54-59, 1986.
2) **Benowitz, N. L.** : Clinical pharmacology of caffeine. Annu. Rev. Med. **41** : 277-288, 1990.
3) **Satoh, H.** and **Vassalle, M.** : Reversal of caffeine-induced calcium overload in cardiac Purkinje fibers. J. Pharmacol. Exp. Ther. **234** : 172-179, 1985.
4) **Satoh, H.** and **Vassalle, M.** : The role of catecholamines on cellular calcium overload induced by caffeine in canine Purkinje fibers. Am. J. Physiol. **257** : H 226-H 237, 1989.
5) **Satoh, H.** : Caffeine depression in spontaneous activity in rabbit sino-atrial node cells. Eur. J. Pharmacol. 1992 (in press).
6) **Satoh, H., Hasegawa, J.** and **Vassalle, M.** : On the characteristics of the inward current induced by calcium overload. J. Mol. Cell. Cardiol. **21** : 5-20, 1989.
7) **Hasegawa, J., Satoh, H.** and**Vassalle, M.** : Induction of the oscillatory current by low concentration of caffeine in sheep cardiac Purkinje fibers. Naunyn-Schmiedeberg's Arch. Pharmacol. **335** : 310-320, 1987.
8) **Rall, T. W.**: Drugs used in the treatment of asthma. *in* The Pharmacological Basis of Therapeutics (Goodman Gilman A., Rall, T. W., Nies, A. S. and Taylor, P., eds.). Chap. 25, ed. by Goodmann Gilman A., Pergamon Press, New York, p618-630, 1990.
9) **Sakuma, A.** : Coffee effect : try at student practice. Jpn. J. Clinc. Pharmacol. **3** : 314-316, 1972.
10) **Sawyer, D. A., Julia, H. L.** and **Turin, A. C.** : Caffeine and human behavior : Arousal, anxiety, and performance effects. J. Behav. Med. **5** : 415-439, 1982.
11) **Lieberman, H. R., Wurtman, R. J., Emde, G. G., Roberts, C.** and **Coviella, I. L. G.** : The effects of low doses of caffeine on human performance and mood. Psychopharmacol. **92** : 308-312, 1987.
12) **Robertson, D., Wade, D., Workman, R., Woosley, R. L.** and **Oates, J. A.** : Tolerance to the humoral and hemodynamic effects of caffeine in man. J. Clin. Invest. **67** : 1111-1117, 1981.
13) **Boulenger, J. P., Patel, J., Post, R. M., Parona, A. M.** and **Marangos, P. J.** : Chronic caffeine consumption increases the number of brain adenosine receptors. Life Sci. **32** : 1135-1142, 1983.
14) **Green, R. M.** and **Stiles, G. L.** : Chronic caffeine consumption sensitizes the A_1 adenosine receptor-adenylate cyclase system in rat cerebral cortex. J. Clin. Invest. **77** : 222-227, 1986.
15) **Horiuchi, K., Mushiake, H.** and **Endo, M.** : Effects of caffeine on arithmetic performance. Jpn. J. Pharmacol. **31** : 164P, 1981.
16) **Robertson, D., Frolich, J. C., Carr, R. K., Watson, J. T.** and **Hollifield, J. W.** : Effects of caffeine on plasma renin activity, catecholamines and blood pressure. N. Engl. J. Med. **298** : 181-186, 1978.
17) **Pincomb, G. H., Lovallo, W. R., Passey, R. B., Whitsett, T. L.** and **Silverstein, S. M.** : Effects of caffeine on vascular resistance, cardiac output and myocardial contractility in young men. Am. J. Cardiol. **56** : 119-122, 1985.
18) **Smith, J. M., Pearson, S.** and **Marks, V.** : Plasma caffeine concentrations in outpatients. Lancet **2** : 985-986, 1982.
19) **LaCroix, A. Z., Mead, L. A., Liang, K., Thomas, C. B.** and **Pearson, T. A.** : Coffee consumption and the incidence of coronary heart disease. N. Engl. J. Med. **315** : 977-982, 1986.
20) **Vandenbroucke, J. P., Kok, F. J., Van't Bosch, G.** and **Van Den Dungen, P. J. C.** : Coffee drinking and mortality in a 25-year follow-up. Am. J. Epidemiol. **123** : 359-361,1986.
21) **Heseltine, D., Dakkak, M.** and **Woodhouse, K.** : The effect of caffeine on postprandial hypotension in the elderly. J. Am. Gerial Soc. **39** : 160-164, 1991.