Cognition enhancers and aging

Chapter 15

Cognition enhancers and aging

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ABSTRACT

Although caffeine is widely recognized as a mild CNS stimulant drug, its consumption might lead to improvement of higher cognitive functions, particularly memory. The present study tests this notion. The scopolamine model of amnesia was used to test the memory-enhancing effects of caffeine, administered as three cups of coffee. Subjects were 16 healthy volunteers who received caffeine 250 mg (three cups of coffee) and nicotine 2 mg separately, in a placebo-controlled, double-blind, cross-over design. Compared to placebo, caffeine and nicotine attenuated the scopolamine-induced impairment of free recall from short-term memory. Caffeine accelerated the recovery from scopolamine-induced impairment of free recall from long-term memory.

A survey conducted among 2,043 people distributed over 5-year age categories ranging from 24 to 86 years showed that more than 90% of all people over 35 years of age consume coffee daily. The estimated daily caffeine intake is lowest in the youngest and oldest age groups. The youngest age groups contain a lower percentage of respondents reporting daily coffee consumption whereas the oldest age groups report a lower daily consumption.

On the basis of these results it was concluded that caffeine, probably the world's most used psychoactive substance, possesses cognition-enhancing properties. Caffeine could be used as a control drug in studies using the scopolamine paradigm and possibly also in other experimental studies of cognitive enhancers, as the effects of a newly developed cognition enhancing drug should at least be superior to those of three cups of coffee.

INTRODUCTION

In the last two decades, there has been rapidly rising in the interest in agents with an influence on cognitive function in the elderly. Bartus, Dean, Beer, and Lippa (1982) formulated the cholinergic hypothesis of

memory dysfunction in old age. This hypothesis has influenced the search for cholinergic mechanisms underlying dementia and has also stimulated the search for drugs which might influence cognition in non-demented elderly. A new class of drugs has been formulated, the majority of which have been explicitly developed with the aim to enhance cognitive function in the aging human brain (Cacabelos, Nordberg, Caamano, Franco-Maside, Fernandez-Novoa, Gomez, et al., 1994). A great number of clinical trials have been conducted to assess the efficacy of these 'Nootropes' or 'Cognition Enhancing Drugs' in the treatment of dementia and Age-Associated Memory Impairment (AAMI) (Crook, Bartus, Ferris, Whitehouse, Cohen, & Gershon, 1986). Unfortunately, research has shown only minor effects of these newly developed substances. It is striking in this respect that one of the most widely used potential cognition enhancers –caffeine– has not received the research interest it deserves. Research until now has mainly focused on caffeine as a CNS stimulant rather than as a cognition enhancer. Jarvis (1993) showed that caffeine may also be a cognition enhancing agent. The present study investigates the potential effect of caffeine in an experimental model of age-related cognitive impairment, the scopolamine model. In addition, coffee and tea consumption in the general population were investigated to determine the amount of caffeine and methylated xanthines ingested in relation to age.

With respect to the rationale behind the present study, one important aspect deals with the proposed action of possible cognition enhancers such as caffeine. Particular experimental models of cerebral aging assume that a temporary state of diminished cognitive functioning will resemble aspects of the cognitive dysfunction found in old age. Diminished cognitive functioning can be induced in young adults by cholinergic blockade as well as by other means (Wesnes, Simpson, & Kidd, 1988; Rusted & Warburton, 1989; Schifano & Curran, 1994). The general hypothesis underlying the search for a cognition enhancing drug is that treatment with such a substance diminishes or reduces the (experimentally induced) cerebral dysfunction and hence restores cognitive function to its optimum. The objective of the present study was, firstly, to measure the scopolamine-induced cognitive dysfunction with tests of memory, information processing, and attention and to try to reverse or attenuate these effects by means of an oral dose of either caffeine or nicotine as a control. Secondly, the use of caffeine in the normal population was measured with the aim to determine the use of caffeine as a 'natural' cognition enhancer in the aged compared to the young population.

MATERIALS AND METHODS

Subjects and procedure in scopolamine experiment

Eight male and eight female volunteers aged 25–35 years participated as subjects in the study. The study was conducted according to a double-blind, double-dummy, placebo-controlled three-way cross-over design with respect to the treatment conditions caffeine 250 mg, nicotine 2 mg, and placebo. Caffeine was administered as three cups of coffee, and nicotine in chewing gum. In the respective placebo conditions, decaffeinated coffee and nicotine-free chewing gum were administered. Furthermore, each session comprised multiple assessments of cognitive function starting at baseline and repeated at 2, 4, and 6 hours after the administration of a body weight-calibrated (0.5 mg/75 kg) dose of subcutaneous scopolamine (adminstration not blinded). The study substance (nicotine, caffeine, placebo) was administered 1 hour after scopolamine. Peak pharmacodynamic effects of all substances were expected to occur at 2 hours after scopolamine. Blood samples to determine plasma levels of caffeine and nicotine/cotinine were taken at that moment.

Psychometry

Several measures of psychological function were obtained. The Verbal Learning Test (Lezak, 1995; Brand & Jolles, 1985) was used to obtain information with regard to memory functioning. Other tests such as choice reaction time, memory scanning, perceptual encoding, focused and divided attention, psychomotor speed, working memory and learning, and long term memory will be described elsewhere (Riedel, Hogervorst, Leboux, Verhey, van Praag, & Jolles, 1995). Visual analogue scales were used to measure subjectively experienced changes as a consequence of drug treatment.

Procedure of population study

An extensive postal survey yielded responses of 2,043 subjects in the Maastricht Aging Study (MAAS). The procedures for subject inclusion and data management have been described extensively in Chapters 3 and 4. For the purpose of the present paper, an analysis was performed on the answers to the following questions in this postal survey: Question 1: "Do you drink coffee? If yes, how many cups per day." and question 2 "Do you drink tea? If yes, how many cups per day". Both questions could be answered by choosing one of five answer categories ranging from: no (0 cups per day), 1-3 cups per day, 4-6 cups per day, 7-10 cups per day, more than 10 cups per day. These categorical responses were transformed into number of cups: 0, 2, 5, 8.5, or 11, in order to obtain estimates of

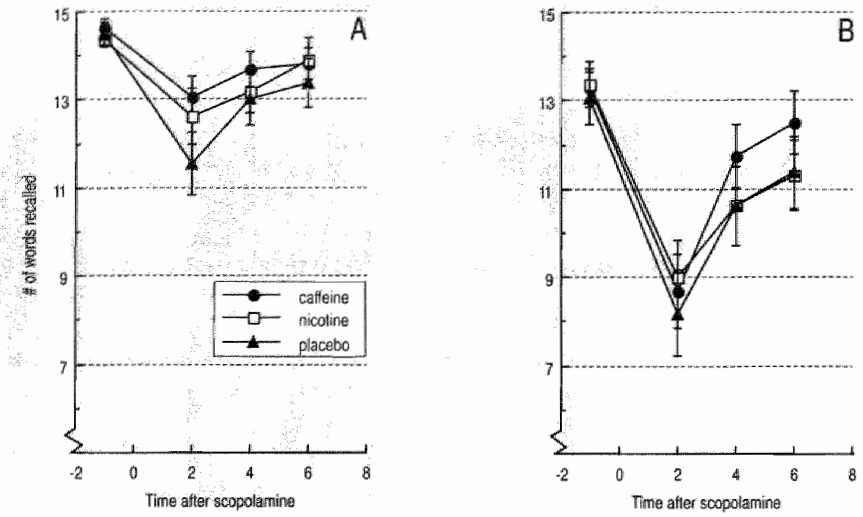

Fig. 15.1.
Time course of the effects of a single subcutaneous administration of 0.5 mg scopolamine/75 kg body weight, combined with 250 mg caffeine in coffee, 2 mg nicotine in chewing gum, and placebo in 16 subjects. X-axis: moment of scopolamine administration, t=–1 refers to baseline, whereas 2, 4 and 6 refer to the hours passed since scopolamine administration. (a) Maximum recall from memory of 15 learned words after 5 trials. (b) Recall from memory of 15 learned words after a delay of 20 minutes.

the average number of cups of coffee consumed per day. The average consumption for each of the 13 age groups (25, 30, 35, ..., 85 years) was then calculated.

RESULTS

Caffeine effects in scopolamine-induced memory deficit

Performance on nearly all cognitive tasks, but most typically on memory tasks was worse after scopolamine. Typical examples of scopolamine-induced cognitive dysfunction are depicted in Figure 15.1. Note from the left graph (Figure 15.1a) that immediate recall on the 15-word learning task, or primary memory performance, was severely impaired 2 hours after scopolamine administration. Caffeine significantly attenuated this effect ($F(1,15)=6.2$, $p<.05$), as did nicotine ($F(1,15)=5.4$, $p<.05$). This was not the case with respect to delayed recall of learned material, or secondary memory performance (Figure 15.1b). Here, caffeine did not attenuate the scopolamine-induced memory dysfunction 2 hours after administration, but caffeine significantly accelerated the recovery from

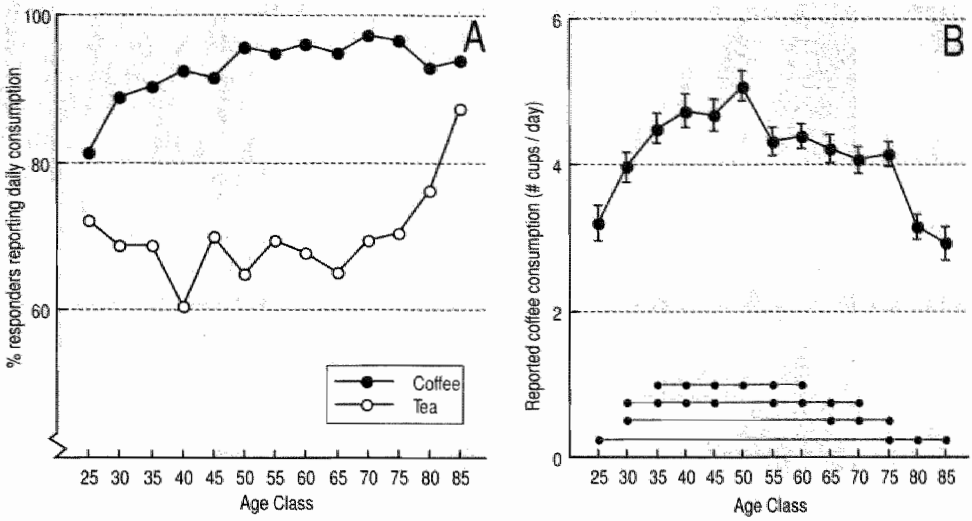

Fig. 15.2.
(a) Daily consumption of coffee (closed circles) and tea (open circles) per age group. (b) Reported mean (*SEM*) number of cups of coffee consumed each day as a function of age in a sample of 1,991 normal subjects divided over 13 age groups ranging from 25-85 years. The result of corrected multiple significance testing between age groups is denoted below: points connected by lines refer to clusters of age groups that are not significantly different.

secondary memory dysfunction 6 hours after scopolamine administration ($F(1,15)=9.8$, $p<.05$).

Caffeine consumption in a sample from the general population

Of the total of 2,043 responses, there were 52 and 85 missing responses as to the reported consumption of coffee and tea, respectively. The distribution of responses by age group can be seen in Figure 15.2. The percentage of respondents reporting coffee and tea consumption is depicted on the left (Figure 15.2a). The estimated average daily coffee consumption is depicted in Figure 15.2b, on the right. Statistical analyses pertain to an n of 1,991 and 1,958 for the reported coffee and tea consumption, respectively. One-way analysis of variance showed that coffee consumption varied significantly between age groups ($F(12,1978)=8.82$, $p<.001$). Multiple range tests using Student-Newman-Keuls correction procedure for multiple t-testing revealed that reported coffee consumption by age showed an inverted U-shape curve (see Figure 15.2b). The subjects' reported average daily coffee consumption was low in the youngest age group (3 cups /day), gradually increased with age and peaked at 50 years (5 cups /day), remained constant until

75 years (4 cups /day), and diminished in the two highest age groups (3 cups /day). We further analysed whether this trend was associated with the same number of consumers drinking different amounts, or whether the number of coffee consumers also varied with age. It appeared that the lower consumption of young people could be explained by a lower percentage of coffee consumers (81% and 88% in the 25 and 30 year groups; all other groups over 90%), whereas the drop in reported consumption in old age appeared to be due to a diminished consumption and not a diminished percentage of consumers. Reported tea consumption was about 2 cups /day overall and varied only slightly, but significantly, between age groups ($F(12,1945)=2.34$, $p<.01$). Multiple range testing yielded no two significantly different age groups.

CONCLUDING REMARKS

This study demonstrated two important findings: (1) Cognitive dysfunction can be pharmacologically modelled by administering a cholinergic antagonist and by assessing performance in the same tasks which are used to assess cognitive aging (see Chapter 4); and (2), caffeine, which is a substance that is used by more than 90% of all people over 35 years of age, possesses cognition enhancing properties. The results were found especially pronounced for memory tasks such as the Verbal Learning Test and not for other variables such as cognitive speed (Riedel et al., 1995). If caffeine would have acted as a CNS stimulant, we were to have expected an effect of caffeine on tapping and on other non-cognitive measures, such as the intercept measures in memory scanning and choice reaction time. It seemed, however, that caffeine displayed a pronounced specificity for memory storage in particular, and, to a lesser extent, for perceptual sensitivity. A possible mechanism of action for caffeine's effect on memory is its antagonism of adenosine (Nehlig, Daval, & Debry, 1992; Stavric, 1992). Adenosine antagonists have been proposed as a class of cognition enhancers for the treatment of age-related cognitive decline and dementia (Briley, 1990; Cacabelos et al., 1994).

As far as we know, this is the first demonstration of caffeine's potential to selectively enhance memory function in subjects who suffer from scopolamine-induced cholinergic dysfunction. Taking into account that cholinergic dysfunction is one of the manifestations of cognitive aging and ultimately Alzheimer's disease, it can be concluded that caffeine consumption might be helpful in preventing or postponing the symptoms of cognitive aging and Alzheimer's disease. In addition, caffeine should be used for comparison in experimental and possibly also clinical trials studying the effects of nootropic- or cognition enhancing drugs.

As yet, there is not enough information about models of cognitive dysfunction. The models currently available, i.e., scopolamine and

hypoxia, possess some predictive validity, but at the same time these models have many limitations (Gamzu, Birkhimer, Hoover, & Gracon, 1990). Therefore it is important to develop new models or new applications of models of cerebral insufficiency. One application is that of the scopolamine model in a challenge paradigm (Sunderland, Tariot, Murphy, Weingarter, Mueller, & Cohen, 1985; Molchan, Martinez, Hill, Weingarter, Thompson, Vitiello, et al., 1992). This means that the model can be used to detect individuals who are particularly vulnerable, in terms of cognitive dysfunction to cholinergic blockade. This approach can be applied to healthy volunteers, but it might make more sense to apply this approach to old individuals who do not have structural damage to the central nervous system. In this way it will be possible to investigate whether people who are compromised by Biological Life Events are more vulnerable to cholinergic blockade than those who have remained free from BLE and whether this effect is dependent upon age. Not only the cholinergic system needs be investigated in this manner, but also other neurotransmitter systems (i.e., 5-HT_3, DA, NA, GABA, glutamate, vasopressin, and possibly combinations of systems) that are considered crucial for the maintenance of cognitive function. Despite the fact that tests to challenge the aforementioned neurotransmitter systems may pose practical and possibly ethical problems, this line of research in cognitive aging will become more important as psychotropic drugs become more and more specific in their effects on neurotransmitter systems.

REFERENCES

Bartus, R. T., Dean, R. L., Beer, B., & Lippa, A. S. (1982). The cholinergic hypothesis of geriatric memory dysfunction. *Science, 217*, 408-417.

Brand, N., & Jolles, J. (1985). Learning and retrieval rate of words presented auditorily and visually. *Journal of General Psychology, 112*, 201-210.

Briley, M. (1990). Biochemical strategies in the search for cognition enhancers. *Pharmacopsychiatry, 2*, 75-80.

Cacabelos, R., Nordberg, A., Caamano, J., Franco-Maside, A., Fernandez-Novoa, L., Gomez, M. J., Alvarez, X. A., Takeda, M., Prous, J., Nishimura, T., & Winblad, B. (1994). Molecular strategies for the first generations of antidementia drugs (1). Tacrine and related compounds. *Drugs of Today, 30*, 295-337.

Crook, T., Bartus, R. T., Ferris, S. H., Whitehouse, P., Cohen, G. D., & Gershon, S. (1986). Age-associated memory impairment: Proposed diagnostic criteria and measures of clinical change: Report of a National Institute of Mental Health Work Group. *Developmental Neuropsychology, 2*, 261-276.

Gamzu, E. R., Birkhimer, L. J., Hoover, T., & Gracon, S. T. (1990). Early human trials in the assessment of cognition activators. *Pharmacopsychiatry, 2*, 44-48.

Jarvis, M. (1993). Does caffeine intake enhance absolute levels of cognitive performance? *Psychopharmacology, 110*, 45-52.

Lezak, M. D. (1995). *Neuropsychological Assessment* (3rd ed.). New York: Oxford University Press.

Molchan, S., Martinez, R. A., Hill, J. L., Weingartner, H. J., Thompson, K., Vitiello, B., & Sunderland, T. (1992). Increased cognitive sensitivity to scopolamine with age and a perspective on the scopolamine model. *Brain Research Reviews, 17*, 215-226.

Nehlig, A., Daval, J-L., & Debry, G. (1992). Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. *Brain Research Reviews, 17*, 139-170.

Riedel, W. J., Hogervorst, E., Leboux, R. L. A. M., Verhey, F. R. J., Praag, H. M. van, & Jolles, J. (In press). Caffeine attenuates scopolamine-induced memory impairment in humans. *Psychopharmacology* .

Rusted, J. M., & Warburton, D. M. (1989). Effects of scopolamine on verbal memory: A retrieval or acquisition deficit? *Neuropsychobiology, 21*, 76-83.

Schifano, F., & Curran, H. V. (1994). Pharmacological models of memory dysfunction? A comparison of the effects of scopolamine and lorazepam on word valence ratings, priming and recall. *Psychopharmacology, 115*, 430-434.

Stavric, B. (1992). An update on research with coffee/caffeine (1989-1990). *Food Chemistry and Toxicology, 30*, 533-555.

Sunderland, T., Tariot, P., Murphy, D. L., Weingartner, H., Mueller, E. A., & Cohen, R. M. (1985). Scopolamine challenges in Alzheimer's disease. *Psychopharmacology, 87*, 247-249.

Wesnes, K., Simpson, P., & Kidd, A. (1988). An investigation of the range of cognitive impairments induced by scopolamine 0.6 mg s.c. *Human Psychopharmacology, 3*, 27-41.