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Full Communication

Brain Factor-7 Extracted from *Bombyx mori* Enhances Cognition and Attention in Normal Children

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ABSTRACT It has been reported that brain factor-7 (BF-7) extracted from *Bombyx mori* improves cognitive functions in normal juveniles and adults as well as cognitively impaired patients. Clinical studies with normal children evaluated the role of BF-7 on brain function in these patients. The objective of this study was to improve cognitive functions of normal schoolchildren with BF-7. Forty-six normal healthy children were divided into two treatment groups: BF-7 (9.9 ± 1.18 years old; 9 boys, 14 girls) and placebo (9.8 ± 1.03 years old; 10 boys, 13 girls). The Color Trails Making Test was used to measure the efficacy of BF-7 on cognition and attention. Results showed that BF-7 reduced the response time by an average of 23% for the Color Trails Making Test. Moreover, BF-7 improved the accuracy of the task around twofold. The results reveal that BF-7 improves brain function for attention and cognitive flexibility in children.

KEY WORDS: • ***attention*** • ***brain factor-7*** • ***children*** • ***cognition*** • ***Color Trails Making Test*** • ***learning and memory***

INTRODUCTION

Learning is defined as "gaining knowledge and comprehension, mastering through experience or study, memorizing or acquiring abilities or skills."[1] The most important cognitive functions that determine learning ability are attention and memory function. Learning ability is also pivotal for success in life because it is related to individual survival, social, occupational, economic, and emotional functions. In school-aged children, repetitious failures in learning could cause the loss of motivation to learn and eventually result in learning deficits. If the child has been left alone or the educational support system has not been available, he or she cannot use his or her intellectual resources and may grow to be incompetent as a social being, which can cause considerable psychological problems and economic and social burdens.[2–4] Educational approaches to improving learning ability and motivation are quite complex. Optimal levels of study objectives, high quality of questions, systematization of learning contents, self-controlled learning activities, and adequate evaluations have been discussed as educational approaches to improve learning capability.[5–7] In addition, positive experiences and feedback through achievements on challenging tasks are considered important educational approaches to enhancing learning motivation.[8–10]

Although studies of educational approaches to increasing learning effectiveness have been conducted, investigations on the effectiveness of biological interventions, including placebo-controlled clinical trials, have been rarely conducted. In animal studies, theanine (γ-glutamylethylamide), catechin,[11,12] taurine,[13] tineapine,[14] rice flavoids,[15] melatonin, FUB 181 (a novel histamine H3-receptor antagonist),[16] bifemelane hydrochloride,[17] and nimodipine[18] have demonstrated neuroprotective properties and efficacy for the enhancement of cognitive functions and learning ability. However, the function of all the above have not been studied in humans.

Recently, it has been reported that brain factor-7 (BF-7), a natural extract from *Bombyx mori*, exerts significant improvement on cognitive and protective functions of the nervous system.[19–25] For example, Lee *et al.*[19] and Kim *et al.*[20] reported that BF-7 enhanced learning and memory function of normal persons in a dose-dependent manner and

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increased the concentration of acetylcholine in rats through a randomized double-blind, placebo-controlled study. Kim *et al.*[20] also showed that BF-7 protected neurons from amyloid β toxicity and oxidative stress. Lee *et al.*[21] reported that BF-7 improved memory function of normal persons and rats and decreased infarct size of hippocampal neurons of rats through a randomized double-blind, placebo-controlled study. It has been suggested that BF-7 improves memory function of normal and demented persons and protects SK-N-SH human neuroblastoma cells from reactive oxidative stress.[22,23] In addition, it was reported that BF-7 improved memory and attention of healthy high school students and significantly attenuated amyloid β induced-apoptosis by decreasing reactive oxygen species accumulation and caspase-like protease activity.[24] Also, it was proposed that BF-7 increased the mean IQ of four individuals from 103 to 114 and increased blood flow in the parahippocampal gyrus and medial temporal area.[25]

Based on the above reports, we conducted this clinical study using the Color Trails Making Test (CTT) with 46 schoolchildren, who were highly ranked academically, to examine whether BF-7 can improve the cognitive functions of concentration and cognition.

SUBJECTS AND METHODS

Preparation of BF-7 and subjects

BF-7 was obtained from the Rural Development Administration in Suwon, Republic of Korea, and prepared as previously described.[26] In brief, *B. mori* and its cocoon were solubilized and proteolyzed with a specific set of proteases, followed by separation and purification of the specific peptide portion using various chromatographies.

Forty-six normal healthy children for study were recruited at Asan Medical Center, Seoul, Republic of Korea, during May 2007, through internet and newspaper advertisement (Table 1) and divided into two groups: BF-7 (9.9 ± 1.18 years old; 9 boys, 14 girls) and placebo (9.8 ± 1.03 years old; 10 boys, 13 girls). Children with autistic disorder and other psychiatric disorders that affect learning, definite intellectual disability, history of brain injury within 1 year, or debilitating neurological or pediatric illnesses were excluded from the study.

Procedures

Demographic and other clinical data were obtained through questionnaires and interviews with both parents and children. The study protocol was approved by the Institutional Review Boards. After informed consents from caretakers and children were obtained, subjects were screened for eligibility using the Korean version of the Kiddie-Schedule for Affective Disorder and Schizophrenia (K-SADS)[27] by a child psychiatrist. Volunteers were randomly distributed into BF-7 and placebo groups by a pharmacist who had no clinical information on the subjects. The color and shape of placebo were the same as the test material. During the study period, investigator, rater, and study participants were double-blinded. Before taking BF-7, baseline assessment including vital signs, height, weight, complete blood count, chemistry, and electrocardiograph were performed. Subjects took 200 mg of BF-7 or placebo twice a day for 16 weeks. Participants visited the clinic every 4 weeks to check unwanted adverse events and drug compliance. Those who omitted study materials more than two times a week were excluded from the study. Final outcome and safety evaluations were conducted at the end of the study.

Measures

K-SADS–Present and Life Time Version (PL)–Korean Version (K-SADS-PL-K).[27] The K-SADS is a semistructured interview for assessing psychiatric diagnoses in children and adolescents. The original K-SADS-Present Version was developed by Puig-Antich and Chambers and noted by Orvaschel *et al.*[28] as a downward extension of the Adult

Table 1. Demographic Characteristics of Children Between Study Groups

	BF-7 (n = *23*)	*Placebo* (n = *23*)	P
Gender [*n* (%)]			.76
Male	9 (39.1)	10 (43.5)	
Female	14 (60.9)	13 (56.5)	
Grade [*n* (%)]			.52
3	5 (13.0)	4 (17.4)	
4	9 (39.1)	6 (26.1)	
5	5 (21.7)	9 (39.1)	
6	6 (26.1)	4 (17.4)	
Paternal educational years [*n* (%)]			.44
≥17	18 (78.3)	20 (87.0)	
13–16	5 (21.7)	3 (13.0)	
10–12	0	0	
7–9	0	0	
≤6	0	0	
Maternal educational years [*n* (%)]			1.00
≥17	15 (65.2)	15 (65.2)	
13–16	8 (34.8)	8 (34.8)	
10–12	0	0	
7–9	0	0	
≤6	0	0	
Economic status [*n* (%)]			.66
Upper class	1 (4.4)	0	
Upper middle class	3 (13.0)	4 (17.4)	
Middle class	15 (65.2)	13 (56.5)	
Lower middle class	4 (17.4)	5 (21.7)	
Lower class	0	1 (4.4)	
Mean IQ (SD)			
Total	115.4 (9.6)	117.9 (10.1)	.39
Verbal	111.7 (24.9)	118.2 (8.3)	.24
Performance	111.0 (11.7)	113.2 (11.5)	.53

The Pearson's χ^2 test and Student's t test were used to compare demographic variables between study groups, and statistical significance was defined as $P < .05$.

Schedule for Affective Disorder and Schizophrenia. It is designed for interviewing both the parent and child and has been updated to be compatible with DSM-III, III-R. After the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) was published in 1994,[29] the K-SADS-PL was introduced by Kaufman *et al.*[30] It was developed from the K-SADS-Present Version. The K-SADS-PL has been used to assess the severity of symptoms as well as the present and lifetime status of 32 DSM-IV child and adolescent psychiatric disorders. In 1997, Kaufman *et al.*[30] reported that the K-SADS-PL was a reliable and valid diagnostic instrument for child and adolescent psychiatric diagnoses. The K-SADS-PL-K is an effective instrument for diagnosing major childhood psychiatric disorders, including attention deficit hyperactivity disorder, behavioral disorders, and tic disorders in Korean children. Its validity and reliability were already established.

CTT. Trail making tests (TMTs) are among the most widely used measures in neuropsychological practice.[31] The CTT allows broader application to cross-cultural studies compared to the original TMT with similar neuropsychological sensitivity.[32] The test consists of two parts, and the score represents the time in seconds spent to complete each part. TMT-A and CTT-1 require the individual to connect numbers in ascending order from 1 to 25 as quickly as possible. TMT-B requires alternation between numbers and letters (1–A, 2–B, 3–C, etc.), while CTT-2 requires alternation between numbers and two colors (1–pink, 2–yellow, 3–pink, etc.).

Statistical analysis

The Pearson's χ^2 test and Student's *t* test were used to compare demographic variables between BF-7 and placebo groups. The repeated measures of multivariate analysis of covariance were used to find changes in mean scores of neurocognitive function tests before and after administration of study materials using the covariates such as intelligence quotient and grade. All statistical analyses were performed using SPSS (Chicago, IL) version 11.0 with statistical significance defined at an α level $< .05$, two-tailed.

Table 2. Results of the CTT Between Before and After Administration of BF-7

	Mean (SD) for BF-7 (n = *23*)		
	Baseline	*End point*	P
CTT-1			
Time	41.6 (17.2)	39.9 (14.3)	<.05
Error	1.09 (1.24)	0.78 (0.95)	<.05
CTT-2			
Time	96.7 (30.6)	74.8 (16.3)	<.05
Error	2.17 (2.01)	1.22 (1.44)	<.05

The repeated measures of multivariate analysis of covariance were used to find changes before and after administration of BF-7, and statistical significance was defined as $P < .05$.

RESULTS

The demographic characteristics of the BF-7 (9.9 ± 1.18 years old; 9 boys, 14 girls) and placebo (9.8 ± 1.03 years old; 10 boys, 13 girls) groups are shown in Table 1. Children with relatively high average level of intelligence (116.7 ± 9.8) were included. There were no significant differences in grade, gender, parental educational status, economic status, and IQ between the BF-7 and placebo groups. The children were clinically examined to measure the TMT and CTT. TMT and CTT measure abilities to connect numbers and

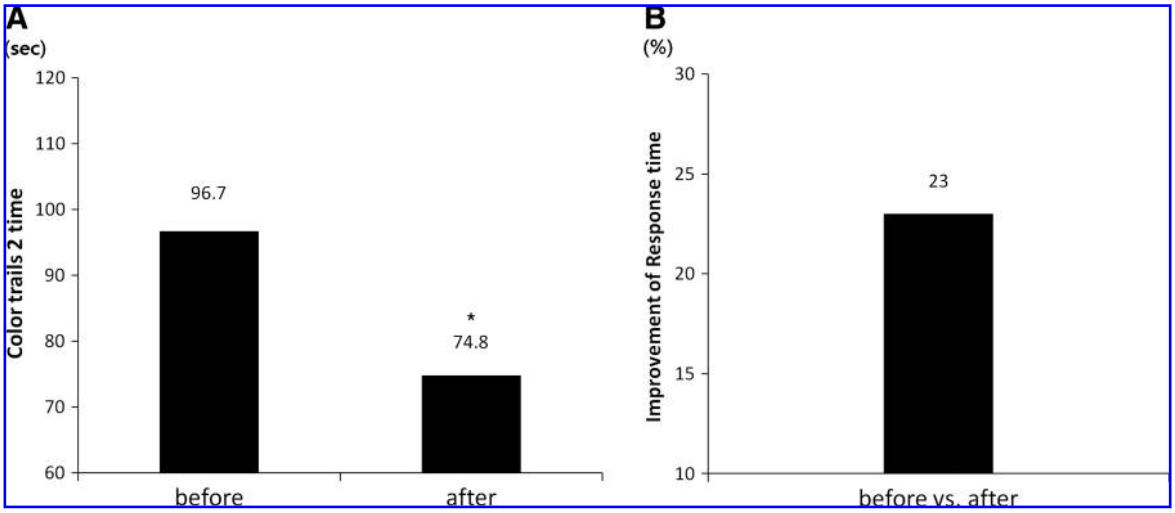

FIG. 1. (**A**) The improvement of response time by BF-7. The CTT-2 response time was determined before BF-7 and after 16 weeks of treatment with 400 mg of BF-7/day. The repeated measures of multivariate analysis of covariance were used to find changes before and after administration of BF-7. Significant differences are shown as $*P < .05$. (**B**) The improvement of response time was evaluated. The percentage of reduced time per baseline is given.

Table 3. Results of the CTT Between BF-7 and Placebo Study Groups

	CTT-2 time			
	BF-7 (n = *23*)		*Placebo* (n = *23*)	
	Baseline	*End point*	*Baseline*	*End point*
Mean (SD) in seconds	96.7 (30.6)	74.8 (16.3)	82.6 (24.8)	74.5 (20.1)
P	<.05		>.05	

The repeated measures of multivariate analysis of covariance were used to find changes before and after administration of BF-7 or placebo, and statistical significance was defined as $P < .05$.

letters in sequence, understanding symbolic meanings of numbers and letters, and whole screen scanning ability. The ability to recognize number and letter symbols is located in the left cerebral hemisphere, and the ability of visual scanning that percept spatial distribution of stimuli is located in the right cerebral hemisphere. Because the performance speed and efficacy of TMT represent general ability of brain function, this test can probe not only visual scanning, attention, and working memory, but also visuomotor coordination. These functions are tightly connected with learning and memory, and study.

The results of the CTT in the BF-7 group are presented in Table 2. The response time of CTT-2 ($t = 4.69$, $df = 22$, $P < .001$) and CTT-2 ($t = 2.55$, $df = 22$, $P = .018$) errors in the BF-7 group were reduced from baseline to end point. The response times before BF-7 treatment (96.7 seconds) and after 16 weeks (74.8 seconds) are shown in Figure 1A. The response time was significantly improved, by 23%, with BF-7 treatment (Fig. 1B). Figure 1 shows that BF-7 significantly reduced the time to conduct the task. In the case of the placebo group, the average response time was reduced by only 9.8% (from 82.6 seconds [baseline] to 74.7 seconds [end point]) (Table 3).

Moreover, the CTT-2 error in the BF-7 group was greatly reduced from 2.17 to 1.22 (Fig. 2A). These results indicate that the error rate was decreased by around 50%. In other words, the accuracy rate in the BF-7 group was improved by twofold (Fig. 2B). These results illustrate that BF-7 enhanced the accuracy of the task by twofold. When these findings are taken together, BF-7 has been shown to improve brain function by conducting tasks more efficiently and precisely. These measures are tightly connected with learning and memory; thus, BF-7 enhanced the learning and memory of children.

DISCUSSION

Many previous reports indicate that BF-7 enhances learning and memory and attention in juveniles and normal adults.[23,24] For example, the memory quotient of both high school-aged juveniles and adults was increased 20–30%.[19] Learning and memory efficiency were enhanced by more than twofold. Also, BF-7 was significantly effective for improving cognitive function of elderly persons. It was suggested that BF-7 might be effective in humans regardless of age. Also, it was reported that it reduced brain stress and prevented dementia. However, so far no clinical studies of BF-7 in children have conducted. In this study, we studied whether BF-7 could enhance brain functions such as learning and memory with normal growing children clinically.

According to these study data, BF-7 reduced the response time for CTT-2 compared with placebo. The CTT-2 is widely employed as a diagnostic tool for evaluating shifts between cognitive sets.[32] It examines the ability to inhibit prepotent responses in favor of less habitual yet more adaptive ones. The ability to switch between cognitive categories, or "sets," is a classical indicator of frontal lobe functioning. The left

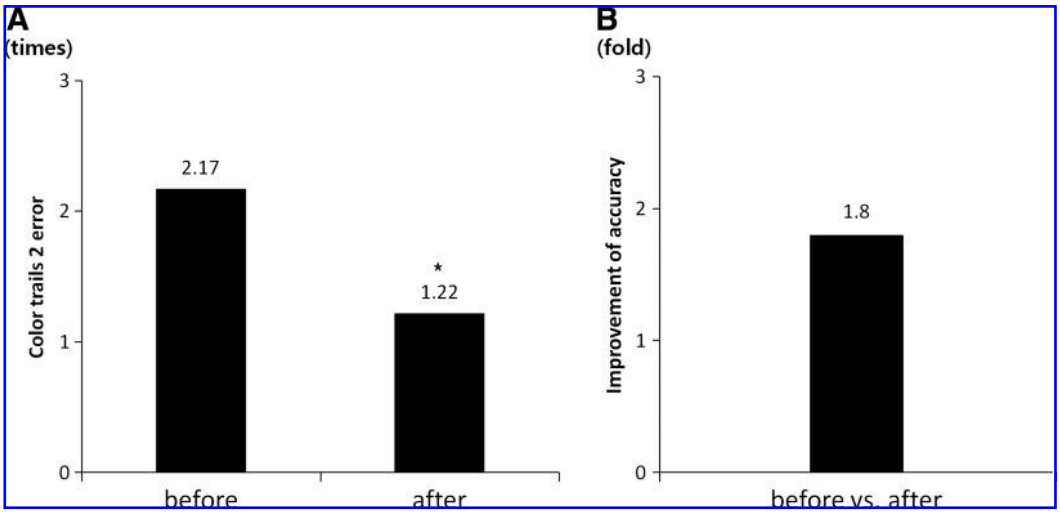

FIG. 2. (**A**) Enhancement of accuracy by BF-7. The CTT-2 error was determined before and after 16 weeks of treatment with 400 mg of BF-7/day. The repeated measures of multivariate analysis of covariance were used to find changes before and after administration of BF-7. Significant differences are shown as $*P < .05$. (**B**) Improvement of accuracy by BF-7. The fold improvement in reduced error per error at baseline is given.

inferior dorsolateral prefrontal cortex seems to be the critical area for eliciting shifts between cognitive sets.[33,34] The role of the inferior dorsolateral prefrontal cortex in providing flexibility to behavior is strengthened by the observation that cognitive inflexibility, or "perseveration," is a core symptom of damage to these areas.[35,36]

The results presented here show that BF-7 is also effective for improving brain functions in children, juveniles, and adults. The average intelligence of subjects in this study was of a high average level. Children with a high level of intelligence might have high cognitive functions, including attention and cognitive flexibility. To obtain any improvement in brain function from individuals of high-level intelligence is relatively difficult compared to normal children. Nevertheless, BF-7 was able to improve brain function in these children with high levels of intelligence.

To our research group's knowledge, no other natural substances have been shown to improve neurological function in human beings, especially in children, except BF-7. This study shows that the enhancement of BF-7 may be quite valuable in clinical settings.

In conclusion, our results clearly showed that BF-7 improved brain function such as attention and cognitive flexibility in normal schoolchildren. Since the safety of BF-7 was already certified, BF-7 is highly recommended as an excellent nutraceutical resource for improving learning and memory of children.

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AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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