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Effect of Circuit Class Training for Eight Weeks on Changes in Ratios of F-Trp/BCAAs and Depression in People with Poststroke Depression

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Abstract. [Purpose] The purpose of the present study was to investigate the potential effects of circuit class training (CCT) on poststroke depression through changes in branched-chain amino acids (BCAAs) (isoleucine, leucine, and valine) and free-tryptophan (f-Trp). [Subjects] The study subjects were 40 stroke patients with major depressive disorder. The subjects were group-matched into an experimental and a control group according to sex, age, height, and weight. [Methods] The experimental CCT group performed gradual task-oriented CCT (80 min per session). The control group performed stretching exercises and weight bearing exercises (80 min per session). Both groups performed the exercises three times per week for eight weeks (24 sessions). Blood samples were collected immediately before the exercise (9:10 a.m.) and after the exercise (10:30 a.m.), every two weeks for eight weeks. [Results] The f-Trp/BCAAs ratio in the CCT group showed a significant increase compared to the control group over time. [Conclusion] The results show that the CCT may help to improve depression in people with poststroke depression (PSD).

Key words: Circuit class training, F-Trp/BCAAs ratios, Poststroke depression

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INTRODUCTION

Poststroke depression (PSD) is regarded as one the most common mental sequela of stroke patients[1)]. PSD patients have low physical and cognitive function, and low self-worth compared to those with no depression[2)], and they have a decreased quality of life[3)]. All these factors can have adverse effects on the functional and mental recovery of stroke patients[4)]. For this reason, various drugs are used to treat PSD, such as tricyclic antidepressant, monoamine oxidase inhibitors, and selective serotonin reuptake inhibitors (SSRIs). However, various adverse reactions to these drugs have been reported, including insomnia, hyposexuality, nausea, and weight gain[5, 6)].

Exercise can relieve the symptoms of depression without the adverse reactions associated with drugs, by increasing the levels of chemicals related to depression, serotonin, dopamine, and norepinephrine, in the hippocampus[7–9)]. In particular, it has been shown that group exercise is more effective than exercising alone[10)]. In this respect, the popularity of circuit class training (CCT), which involves task-oriented exercise in groups, is growing. CCT has been reported to have many benefits, such as improving the mobility of stroke patients and shows better cost efficiency than other therapies[11, 12)]. Most studies of CCT, however, have focused on the improvement of balance, walking ability, or upper extremity functions, and few studies have investigated the potential effects of group CCT on depression. Accordingly, this study was conducted to investigate the potential effects of CCT on depression through changes in branched-chain amino acids (BCAAs) (isoleucine, leucine, and valine) and free-tryptophan (f-Trp).

SUBJECTS AND METHODS

The study subjects were stroke patients who were diagnosed with major depressive disorder and dysthymic disorder according to DSM-IV[13)] guidelines following hospitalization and treatment at D Hospital in Busan. The degree of depression symptoms was measured with the Beck Depression Inventory (BDI), which is the most widely used self-report measure of depression. Forty subjects who had moderate depression, defined as a BDI score between 19 and 29, were selected for inclusion in this study[14)]. Additional selection criteria were: absence of cognitive problems such as dementia, aphasia, or dysarthria; a score of 23 or higher on the Mini-Mental State Examination; absence of other men-

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tal problems except depression; absense of acute musculoskeletal problems; and an ability to walk 10 m with no physical help. Furthermore, those who had taken or were taking antidepressants such as SSRIs prior to the onset of stroke were excluded. Subjects were at least six months since the onset of stroke. The subjects were group-matched into an experimental group and a control group according to sex, age, height, and weight. The experimental CCT group performed gradual task-oriented CCT (80 min per session) and received 30 min of general physical therapy. The control group performed stretching exercises and weight-bearing exercises (80 min per session)[15]. They also received 30 min of general physical therapy. The CCT was performed three times per week for eight weeks (24 sessions). The sessions included eight different workstations. The total CCT consisted of four steps: warming up (5 min), circuit training (60 min), evaluation and a short break (10 min), and a group game (15 min). The control group also performed warming up for 5 min before exercise and cooling down for 10 min after the exercise. Two physical therapists received one day of training before this program, and data on the participants' attendance and adverse events (such as falls and heart problems) were collected during the experiment[16]. Preliminary training for the whole program was performed one day before the start of the intervention. BDI scores were measured before the start of the experiment and again after eight weeks, at the end of the experiment.

Blood sampling was performed as follows:

A catheter was installed in the forearm vein of the subjects, and 5 mL was collected immediately before the exercise (9:10 am) and immediately after the exercise (10:30 am) at D1 (the start), D6 (two weeks), D12 (four weeks), D18 (six weeks), and D24 (eight weeks). The blood samples were centrifuged (3,000 rpm × 15 min) and stored in a refrigerator (−82°C) until they were analyzed. The f-Trp, (i.e., not combined with albumin) was separated from the plasma using a modified version of the method of Bloxam and Hutson et al[17].

To analyze the BCAAs and f-Trp, the amino acids were sampled with an acetonitrile/methanol solution and diluted to another concentration by an internal standard (norleucine and D5-Trp; Cambridge Isotope Laboratories, Andover, MA). The plasma concentration was then analyzed by high performance liquid chromatography (Pharmacia, USA).

For the data analysis, the statistics package SPSS 18.0 was used. The normality of the distribution of the data was tested with the Kolmogorov–Smirnov test. Changing trends over time in each group were examined using a two-way repeated measures ANOVA. The paired *t*-test was used to examine intragroup variations over time, and the independent t-test was used to examine intergroup variations. The statistical significance level was used 5% (Significance was accepted for values of $p < 0.05$).

All the patients gave their written consent after receiving an explanation about the experiment and had been cautioned about potential adverse effects of this experiment. The experiment was approved by the Human Subject's Research Ethics Committee of the Catholic University of Pusan (CUPIRB-2013-019).

RESULTS

The independent t-test for the intergroup comparison of general characteristics did not show any significant differences (Table 1). The changes in f-Trp, BCAAs, and f-Trp/BCAAs ratios in the blood after the performance of the CCT or the extension/weight movement exercise for 80 min by each group are shown in Table 2.

Before the intervention, the concentrations of f-Trp, BCAAs, and the f-Trp/BCAAs ratio in the blood showed no differences between the groups. However, intergroup differences of f-Trp ($F = 10.457$, $p = 0.00$), BCAAs ($F = 10.847$, $p = 0.00$), and f-Trp/BCAAs ($F = 3.157$, $p = 0.00$) after the intervention were significant. In the CCT group, after CCT, f-Trp significantly increased from the first day of the CCT (D1), and it remained increased at two weeks (D6), six weeks (D18), and eight weeks (D24) ($F = 17.635$, $p = 0.00$). There were no significant differences in f-Trp between week one (D1) and two weeks (D6) and between six weeks (D18) and eight weeks (D24). The control group showed no significant changes over time. The values of the BCAAs in the CCT group showed a significant decrease over time ($F = 10.237$, $p = 0.00$) immediately after the start of the exercise, but no significant difference between six weeks (D18) and eight weeks (D24)was observed. The f-Trp/BCAAs ratios also showed a significant increase only in the CCT group ($F = 27.277$, $p = 0.00$). In addition, in contrast to the control group, the BDI score of the CCT group exhibited a significant decrease in the final week (D24) compared to the first day of the exercise (D1) from 21.35±2.28 to 17.65±1.57 (t=5.07, p=0.00) (Table 3).

DISCUSSION

This study investigated the effects of CCT on the amelioration of depression in chronic stroke patients who had moderate depression symptoms. In particular, changes in the f-Trp/BCAAs ratio, which can indirectly determine the level of brain serotonin, an indicator of depression, was measured over eight weeks.

BCAAs (isoleucine, leucine, and valine) are essential amino acids, which cannot be synthesized by the body. Theoretically, they increase in response to the decomposition of proteins in the body, and they are decomposed again and oxidized to energy sources through the same metabolic process used for carbohydrates and fatty acids[18]. In contrast to most general amino acids, which are oxidized in the liver, the amino acids derived from BCAAs are oxidized mainly in the skeletal muscles[19]. Therefore, the use of BCAAs increases in the muscles during recovery after exercise. This decreases the concentration of BCAAs in plasma and thereby increases the f-Trp/BCAAs ratio. For the CCT group in this study, the plasma concentration of BCAAs after CCT was significantly lower than prior to the exercise, and the concentration of BCAAs after exercise decreased over time. This finding is likely due to increased use of BCAAs to improve the recovery rate of fatigued muscles in the recovery process over time.

Trp is a precursor of serotonin that is converted into serotonin in the brain. However, as the percentage of f-Trp

Table 1. General characteristics of the subjects (n=40)

Group	CCT (n=20)	CON (n=20)
Sex	Men 7 (35%): Women 13 (65%)	Men 7 (35%): Women 13 (65%)
Age	57.2±10.8	58.7±9.7
Height (cm)	163.09±7.1	165.4±5.2
Weight (kg)	66.40±11.9	68.1±5.9
BMI (kg/m^2)	24.02±5.7	25.0±4.2
Paretic side	Rt 11 (55%): Lt 9 (45%)	Rt 12 (60%): Lt 8 (40%)
Type	Infarction 14 (70%): Hemorrhage 6 (30%)	Infarction 11 (55%): Hemorrhage 9 (45%)
Duration (Mon)	8.4±1.9	7.9±2.6

Table 2. Responses of blood chemicals to circuit exercise test over time

			D1	D6	D12	D18	D24
f-Trp (μmol/L)	Pre	CCT	54.5±2.46	54.83±2.62	54.21±2.22	54.67±2.89	54.06±1.89
		CON	53.99±2.82	54.62±2.55	54.99±2.37	55.09±2.07	55.89±2.03
	Post	CCT	60.16±2.28^a	60.79±2.67^a	62.66±3.07^b	64.50±3.19^c	65.50±3.29^c
		CON	54.46±1.95	54.24±2.27	54.51±1.74	54.76±1.82	54.37±1.55
BCAAs (μmol.L-1)	Pre	CCT	540.80±28.22	538.60±25.43	533.37±18.14	534.48±11.89	535.30±13.37
		CON	535.81±19.45	539.01±12.49	540.98±12.96	539.69±12.26	540.68±11.84
	Post	CCT	496.53±13.71^a	488.75±11.88^b	478.18±11.39^c	471.78±12.37^d	470.51±14.00^d
		CON	533.81±8.71	533.86±10.97	538.21±12.41	536.37±14.48	539.43±11.78
Trp/BCAAs (×10–2)	Pre	CCT	1.00±0.06	1.02±0.07	1.01±0.05	1.02±0.06	1.01±0.04
		CON	1.00±0.06	1.01±0.05	1.01±0.05	1.02±0.05	1.01±0.05
	Post	CCT	1.21±0.06^a	1.24±0.06^b	1.31±0.07^c	1.37±0.08^d	1.39±0.09^e
		CON	1.02±0.03	1.01±0.04	1.01±0.04	1.02±0.04	1.00±0.03

(Mean ±SD) ^{a,b,c,d,e}Different superscripts within the same rows represent significant differences. ($p<0.05$), D1: the first day of circuit exercise), D6 (two weeks of circuit exercise), D12 (four weeks of circuit exercise), D18 (six weeks of circuit exercise), and D24 (eight weeks of circuit exercise)

Table 3. Comparison of BDI scores between CCT group and Control group

	Group	Pre-test (D1)	Post-test (D24)
BDI (score)	CCT (n=20)	21.4±2.3	17.7±1.6^a
	CON (n=20)	22.1±2.4	20.1±2.1^b

(Mean ±SD) ^{a,b}Different superscripts represent significant differences. ($p<0.05$)

under stable conditions is only 10% of the total Trp, it is difficult to convert it into brain serotonin. It has been reported, however, that long-term exercise could help to increase the level of serotonin in the brain by increasing the concentration of f-Trp[20]. The results of the CCT group in the present study provide evidence in support of this hypothesis. Long-term CCT is believed to increase the concentration of f-Trp, which then increases the catecholamine level in the blood while decreasing insulin and glucose levels. This causes an increase in lipocyte-induced free fatty acids in plasma. As a result, Trp, which strongly combines with albumin, is replaced with f-Trp. The latter then combines loosely with albumin, and the level of f-Trp in plasma increases. Due to increase in f-Trp and decrease in BCAAs over time, the concentration of f-Trp in plasma is expected to rise and aid the competitive passage of f-Trp through the cerebrovascular barrier with the help of the amino acid carrier (system L)[21]. Subsequently, the concentrations of Trp and serotonin in the brain would increase.

Consequently, we believed that the ratio of f-Trp/BCAAs increased over time in the CCT group in this study, and that this increase enhanced the concentrations of Trp and serotonin in the brains of the subjects in the CCT group, likely contributing to the improvement in depression as shown by their BDI scores.

Limitations of this study were that the subjects were limited to those with moderate depression, and dietary adjustments that could have affected the plasma amino acids were not taken into account. Furthermore, although it has been reported that the f-Trp/BCAAs ratio affects central fatigue,

this was not considered.

Future studies on central fatigue and PSD could contribute to the clarification of the effects of the f-Trp/BCAAs ratio on PSD. In conclusion, this study found that CCT exercise for eight weeks increased the f-Trp/BCAAs ratio and might help improve PSD.

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