Sogeunjung-tang improves depressive-like behavior decreased by forced-swimming test

Hyun-Ja Jeong¹, A Rim Moon¹, Na-Hyung Kim², Cha-kwon Chung³*

¹Department of Food Science & Technology, Hoseo University, 20, Hoseo-ro 79beon-gil, Baebang-eup, Asan, Chungcheongnam-do 31499, Republic of Korea; ²Department of Pharmacology, College of Korean Medicine, Kyung Hee University, 26, Kyungheedae-ro, Dongdaemun-gu, Seoul, 02447, Republic of Korea; ³Department of Food & Nutrition, Hallym University, Chuncheon, 200-702, Republic of Korea.

INTRODUCTION

Depression is one of the world’s leading disabilities, and as measured over the years, large numbers of people are getting afflicted by this disabling condition (Chang and Fava, 2010; McKenna et al., 2005). The forced swimming test (FST) is commonly used as a screening test for antidepressant properties of drugs and also as an endurance test to examine antifatigue effects of candidate agents (De-Mello et al., 1992; Kim et al., 2008; Porsolt et al., 1978). Glucose, blood urea nitrogen (BUN), lactate dehydrogenase (LDH), creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total protein are blood biochemical parameters related to depression and fatigue. Energy for exercise is derived initially from the breakdown of glycogen and, later, from circulating glucose released by the liver and from nonesterified fatty acids (Dorchy, 2002). As is commonly known, glucose levels are decreased immediately after exercise. The BUN test is a routine test used primarily to evaluate renal function. Serum LDH and CK are known to be accurate indicators of muscle damage. Total protein is a rough measure of serum protein. Protein measurements can reflect nutritional state, kidney disease, liver disease, and many other conditions (Dorchy, 2002). FST exposure produces a variety of time-dependent neurochemical, endocrine, and immune alterations in the rat (Connor et al., 1997). Following related animal studies, repeated administration of drugs daily for 14 days resulted in the demonstration of antidepressant activity at doses lower than those which were previously necessary to demonstrate activity when the drugs were administered over a period of 24 h (Lifschytz et al., 2006). Antidepressants such as monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and tricyclic antidepressants have been used in the clinic for several decades (Kim et al., 2002). Sogeunjung-tang (S-tang) is a traditional Korean medicine that has been used for the treatment of anxiety disorder. However, its mechanism of action remains unknown. In the current study, we examined the immobility time and blood biochemical parameters after FST to investigate the anti-depressant effect of S-tang.

MATERIALS AND METHODS

Animals

The original stocks of male ICR mice (4-week-old) weighing 13 - 15 g were purchased from the Dae-Han Experimental Animal Center (Daejon, Korea), and were maintained at the Department of Food & Nutrition, Hallym University. The mice were housed in a laminar-airflow room maintained at a temperature of 22 ± 1°C and relative humidity of 55 ± 10% throughout the study, respectively. No animal was used more than once. Food and water were available ad libitum. All protocols were approved by the institutional animal care and use committee of Kyung Hee University (KHUASP(SE)-10-032).

Preparation of S-tang

The S-tang was obtained from Noa drug store (Seoul, Korea). S-tang is composed of 6 oriental herbs containing of...
Table 2. Value of blood biochemical parameters

|                  | CON          | Fluoxetine | ST 10 mg/kg | ST 100 mg/kg |
|------------------|--------------|------------|-------------|--------------|
| Glucose (mg/dL)  | 218.00 ± 3.06| 232.67 ± 25.44 | 227.33 ± 42.90 | 226.67 ± 42.90 |
| Total protein (g/dL) | 5.57 ± 0.15 | 5.73 ± 0.12 | 5.57 ± 0.07 | 5.43 ± 0.07 |
| LDH (IU/L)       | 1781.00 ± 412.35 | 779.00 ± 106.31* | 1657.67 ± 249.76 | 818.67 ± 108.69* |
| BUN (mg/dL)      | 15.73 ± 0.44 | 18.70 ± 0.47 | 16.07 ± 0.84 | 15.90 ± 0.65 |
| CK (mg/dL)       | 1428.67 ± 577.75 | 749.67 ± 113.59* | 1549.67 ± 707.47 | 461.00 ± 88.04* |

CON: saline administered control group, ST: S-tang orally administered group. Values represent the mean ± SEM. *p < 0.05: significantly different from the control group.

Blood biochemistry analysis

After the last FST, the mice were anesthetized with an intraperitoneal injection of ketamine (80 mg/kg) and xylazine (4 mg/kg) and blood (1 ml) was withdrawn from the heart of the mice into syringes. Serum was then prepared by centrifugation at 1500 × g at a temperature of 4 °C for 10 min. The BUN, CK, LDH, glucose, and total protein contents were determined by an autoanalyzer (Hitachi 747, Hitachi, Japan).

Statistical analysis

The results were expressed as mean ± S.E.M. for the number of experiments. Statistical significance was compared among each group and by the ANOVA with post-hoc multiple comparison test. Results with p < 0.05 were considered statistically significant.

RESULTS

Effect of S-tang oral administration or pharmaceutical acupuncture on the FST

To estimate the anti-depressant effect of S-tang, we measured immobility time on FST. The immobility time of the S-tang oral administration or pharmaceutical acupuncture group at 14 days was significantly decreased in comparison with the control group (Figure 1). The anti-depressant effect of S-tang was higher than that of fluoxetine (a classical antidepressant).

Effect of S-tang oral administration on blood biochemical parameters

In Figure 1, S-tang oral administration and pharmaceutical acupuncture showed the anti-depressant effect. Therefore, we analyzed the glucose, total protein, LDH, BUN, and CK level in serum. As shown in Table 1, the LDH and CK content of the serum in the fluoxetine and S-tang100 mg/kg treated groups was decreased significantly in comparison with that of the control group (p < 0.05). But S-tang or fluoxetine did not affect the glucose, total protein, and BUN levels compared with the control group.

DISCUSSION

As is already described in the materials and methods section, S-tang consists of 6 different herbs. Mao et al. (2008a) reported anti-depressant-like effect of ethanol extract from Paeonia lactiflora in mice. They also reported that administration of total glycosides of peony (paenonilin and albiflorin) caused a significant reduction of immobility time in both the FST and tail suspension tests (Mao et al., 2008b). Wang et al. reported that liquiritin and isoliquiritin, isolated from Glycyrrhiza uralensis have an anti-depressant-like effect in the FST and tail

S. tang

Pharmacological studies

S-tang (20 μl) was subcutaneously injected into the right Taiyuan acupoint (LU-9) located on the anterolateral aspect of the wrist, between the radial styloid process and the scaphoid bone, in the depression ulnar to the abductor pollicis longus tendon (WHO Regional office for the Western Pacific, 2008). LU-9 is one of the most commonly used acupuncture points to tonify the vital energy and regulate the immune system (Zhou et al., 2012). The anatomical location of the LU-9 in mice is equivalent to that described in humans and the location of this acupoint was identified based on the description provided by Stux and Pomeranz (Stux and Pomeranz, 1987). Animals in the control group received an injection of saline into the same site.

FST

After the first measurement of the immobility time, the mice (n = 5/group) were divided into the control group, fluoxetine group, S-tang oral administration (10 and 100 mg/kg) group, and S-tang pharmaceutical acupuncture (10 and 100 mg/kg) group to match the swimming time in each group. These drugs were administered into mice once per day for 2 weeks. Fluoxetine, known as a classical anti-depressant, was used as a reference agent. During a 6 min FST, the duration of immobility was measured as previously described by Porsolt et al. (1977). The apparatus used for this test consisted of two Plexiglas cylinders (height 25 cm, diameter 10 cm) placed side by side in a Makrolon cage filled with water (10 cm height) at 23 - 25 °C. Two mice were tested simultaneously for 6 min inside vertical Plexiglas cylinders; a non-transparent screen placed between the two cylinders prevented the mice from seeing each other. The total duration of immobility, after a delay of 2 min, was measured during a period of 4 min. Each mouse was considered to be immobile when it ceased struggling and remained floating motionless in the water, making only those movements necessary to keep its head above water.

TANG / www.e-tang.org

2017 / Volume 7 / Issue 1 / e4
In our study, S-tang acute kidney injury (Ferquson et al., 2008). The creatine-creatine phosphate concentrations in the blood of the mice were examined after the FST. The result of this study indicates that the serum concentrations of the intramuscular enzymes such as CK and LDH, which were increased by the FST, decrease significantly with S-tang treatment. Therefore, these results suggest that S-tang regulate the blood biochemical parameters related to depression in blood.

Conclusively, it was found for the first time that S-tang decreases the immobility time after FST in mice. Moreover, this treatment tends to improve the levels of several blood biochemical parameters such as LDH and CK after FST. These results indicate that S-tang may have beneficial applicability as a potential anti-depressant agent.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Bessman SP, Carpenter CL. The creatine-creatine phosphate energy shuttle. Annu Rev Biochem. 1985;54:831-862.

Chang T, Fava M. The future of psychopharmacology of depression. J Clin Psychiatry. 2010;71:971-975.

Connor TJ, Kelly JP, Leonard BE. Forced swim test-induced neurochemical endocrine and immune changes in the rat. Pharmacol Biochem Be. 1997;58:961-967.

Coombes JS, McNaughton LR. Effects of branched-chain amino acid supplementation on serum creatine kinase and lactate dehydrogenase after prolonged exercise. J Sports Med Phys Fitness. 2000;40:240-246.

Costill DL, Fink WJ. Plasma volume changes following exercise and thermal dehydration. J Appl Physiol. 1974;37:521-525.

De-Mello MA. Effect of exercise during pregnancy and damage on maternal blood chemistry and fetal growth. Braz J Med Biol Res. 1992;25:537-542.

Dorothy H. Sports and type I diabetes: personal experience. Rev Med Brux. 2002;23:A211-217.

Ferquson MA, Vaidya VS, Bonventre JV. Biomarkers of nephrotic acute kidney injury. Toxicology. 2008;245:182-193.

Effect of S-tang on depression

Fig.1. Effect of S-tang oral administration or pharmaceutical acupuncture on the FST. The S-tang oral administration or pharmaceutical acupuncture continued for 14 days at the same time every morning. During the FST, S-tang oral administration or pharmaceutical acupuncture was conducted 1 h before the test. Values are the means ± SEM. *p < 0.05 vs. a saline-treated control group. CON, saline-administered control group; Flu, Fluoxetine (10 mg/kg)-administered group; ST10, S-tang (10 mg/kg)-administered group; ST100, S-tang (100 mg/kg)-administered group; OA, oral administration; PA, pharmaceutical acupuncture.

nephrotoxic acute kidney injury. Toxicology. 2008;245:182-193.

spatial orientation

spatial memory

stress increases the serum concentrations of the intramuscular enzymes CK and LDH. Glucose plays an important role as the main source of energy during exercise or in the case of starvation (Rose and Sampson, 1982). When exercising or in the case of starvation, liver glycogen reserves and gluconeogenesis appears to maintain blood glucose levels in the body. Moreover, the glucose level generally decreases immediately after the FST. Total protein measurements can reflect the nutritional state, kidney disease and chronic liver disease and it can also indicate the condition between the extracellular and intracellular fluids (Costill and Fink, 1974).

During digestion, protein is broken down into amino acids. Thus, the BUN, CK, LDH, glucose, total protein, and albumin contents in the blood of the mice were examined after the FST. The BUN, CK, LDH, glucose, total protein, and albumin contents in the blood of the mice were examined after the FST. The result of this study indicates that the serum concentrations of the intramuscular enzymes such as CK and LDH, which were increased by the FST, decrease significantly with S-tang treatment. Therefore, these results suggest that S-tang regulate the blood biochemical parameters related to depression in blood.

Conclusively, it was found for the first time that S-tang decreases the immobility time after FST in mice. Moreover, this treatment tends to improve the levels of several blood biochemical parameters such as LDH and CK after FST. These results indicate that S-tang may have beneficial applicability as a potential anti-depressant agent.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Bessman SP, Carpenter CL. The creatine-creatine phosphate energy shuttle. Annu Rev Biochem. 1985;54:831-862.

Chang T, Fava M. The future of psychopharmacology of depression. J Clin Psychiatry. 2010;71:971-975.

Connor TJ, Kelly JP, Leonard BE. Forced swim test-induced neurochemical endocrine and immune changes in the rat. Pharmacol Biochem Be. 1997;58:961-967.

Coombes JS, McNaughton LR. Effects of branched-chain amino acid supplementation on serum creatine kinase and lactate dehydrogenase after prolonged exercise. J Sports Med Phys Fitness. 2000;40:240-246.

Costill DL, Fink WJ. Plasma volume changes following exercise and thermal dehydration. J Appl Physiol. 1974;37:521-525.

De-Mello MA. Effect of exercise during pregnancy and damage on maternal blood chemistry and fetal growth. Braz J Med Biol Res. 1992;25:537-542.

Dorothy H. Sports and type I diabetes: personal experience. Rev Med Brux. 2002;23:A211-217.

Ferquson MA, Vaidya VS, Bonventre JV. Biomarkers of nephrotic acute kidney injury. Toxicology. 2008;245:182-193.

spatial orientation

spatial memory

spatial orientation

spatial memory

stress increases the serum concentrations of the intramuscular enzymes CK and LDH. Glucose plays an important role as the main source of energy during exercise or in the case of starvation (Rose and Sampson, 1982). When exercising or in the case of starvation, liver glycogen reserves and gluconeogenesis appears to maintain blood glucose levels in the body. Moreover, the glucose level generally decreases immediately after the FST. Total protein measurements can reflect the nutritional state, kidney disease and chronic liver disease and it can also indicate the condition between the extracellular and intracellular fluids (Costill and Fink, 1974).

During digestion, protein is broken down into amino acids. Thus, the BUN, CK, LDH, glucose, total protein, and albumin contents in the blood of the mice were examined after the FST. The BUN, CK, LDH, glucose, total protein, and albumin contents in the blood of the mice were examined after the FST. The result of this study indicates that the serum concentrations of the intramuscular enzymes such as CK and LDH, which were increased by the FST, decrease significantly with S-tang treatment. Therefore, these results suggest that S-tang regulate the blood biochemical parameters related to depression in blood.

Conclusively, it was found for the first time that S-tang decreases the immobility time after FST in mice. Moreover, this treatment tends to improve the levels of several blood biochemical parameters such as LDH and CK after FST. These results indicate that S-tang may have beneficial applicability as a potential anti-depressant agent.

ACKNOWLEDGEMENTS

None.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES

Bessman SP, Carpenter CL. The creatine-creatine phosphate energy shuttle. Annu Rev Biochem. 1985;54:831-862.

Chang T, Fava M. The future of psychopharmacology of depression. J Clin Psychiatry. 2010;71:971-975.

Connor TJ, Kelly JP, Leonard BE. Forced swim test-induced neurochemical endocrine and immune changes in the rat. Pharmacol Biochem Be. 1997;58:961-967.

Coombes JS, McNaughton LR. Effects of branched-chain amino acid supplementation on serum creatine kinase and lactate dehydrogenase after prolonged exercise. J Sports Med Phys Fitness. 2000;40:240-246.

Costill DL, Fink WJ. Plasma volume changes following exercise and thermal dehydration. J Appl Physiol. 1974;37:521-525.

De-Mello MA. Effect of exercise during pregnancy and damage on maternal blood chemistry and fetal growth. Braz J Med Biol Res. 1992;25:537-542.

Dorothy H. Sports and type I diabetes: personal experience. Rev Med Brux. 2002;23:A211-217.

Ferquson MA, Vaidya VS, Bonventre JV. Biomarkers of nephrotic acute kidney injury. Toxicology. 2008;245:182-193.
Effect of S-tang on depression

Kim NH, Jeong HJ, Lee JY, Go H, Ko SG, Hong SH, Kim HM, Um JY. The effect of hydrolyzed Spirulina by malted barley on forced swimming test in ICR mice. Int J Neurosci. 2008;118:1523-1533.

Lifschytz T, Shalom G, Lerer B, Newman ME.. Sex-dependent effects of fluoxetine and triiodothyronine in the forced swim test in rats. Eur Neuropsychopharmacol. 2006;16:115-121.

Mao Q, Huang Z, Ip S, Che C. Antidepressant-like effect of ethanol extract from Paonia lactiflora in mice. Phytother Res. 2008a;22:1496-1499.

Mao QQ, Ip SP, Tsai SH, Che CT. Antidepressant-like effect of peony glycosides in mice. J Ethnopharmacol. 2008b;119:272-275.

Marar IE, Amico JA. Vasopressin, oxytocin, corticotrophin-releasing factor, and sodium responses during fluoxetine administration in the rat. Endocrine. 1998;8:13-18.

McKenna MT, Michaud CM, Murray CJ, Marks JS. Assessing the burden of disease in the United States using disability-adjusted life years. Ame J Preven Med. 2005;28:415-423.

Naitoh H, Yamaoka K, Nomura S. Behavioral assessment of antidepressants (1) The forced swimming test: a review of its theory and practical application. Yakubutsu Seishin Kodo. 1992;12:105-111.

Porsolt RD, Anton G, Blavet N, Jalfre M.. Behavioural despair in rats: a new model sensitive to antidepressant treatments. Eur J Pharmacol. 1978;47:379-391.

Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: a primary screening test for antidepressants. Arch Int Pharmacodyn Ther. 1977;229:327-336.

Rose RJ, Sampson D. Changes in certain metabolic parameters in horses associated with food deprivation and endurance exercise. Res Vet Sci. 1982;32:198-202.

Shin HY, Shin TY, Seo SW, Na HJ, Kwon YT, Song BK, Lee EJ, Kim YK, Hong MC, Shin MK, Hong SH, Kim HM. Decrease of immobility behavior in forced-swimming test and immune system enhancing effect of traditional medicine Gamisipjundaebotang. Pharmacol Biochem Behavior. 2004;79:253-259.

Stux G, Pomeranz B. Acupuncture, Textbook and Atlas. Berlin/Heidelberg, GSpringer–Verlag. 1987;1-34.

Van der Veen KJ, Willebrands AF. Isoenzymes of creatine phosphokinase in tissue extracts and in normal and pathological sera. Clin Chim Acta. 1966;13:312-316.

Vasudevan G, Mercer DW, Varat MA. Lactic dehydrogenase isoenzyme determination in the diagnosis of acute myocardial infarction. Circulation. 1978;57:1055-1057.

Wang W, Hu X, Zhao Z, Che CT. Antidepressant-like effects of liquiritin and isoliquiritin from Glycyrrhiza uralensis in the forced swimming test and tail suspension test in mice. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1179-1184.

WHO Regional Office for the Western Pacific. WHO Standard Acupuncture Point Locations in the Western Pacific Region. Manila, World Health Organization. 2008.

Zhao Z, Wang W, Guo H, Zhou D. Antidepressant-like effect of liquiritin from Glycyrrhiza uralensis in chronic variable stress induced depression model rats. Behav Brain Res. 2008;194:108-113.

Zhou Y, Shen XY, Wang LZ, Wei JZ, Cheng K. The infrared radiation spectrum of acupoint taimyuan (LU 9) in asthma patients. J Tradit Chin Med. 2012;32:187-192.