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Stress-Reducing Effects of Brown Rice *Koji*

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Abstract The primary objective of this study is to determine whether a diet supplemented with brown rice *koji* (BRK) results in a reduced stress response in rats and mice. BRK, which has been suggested as a candidate for use as a stress- and fatigue-fighting supplement, was compared with red ginseng extract (RG) for its stress-reducing potential. The animals in this study were divided into no-stress, stress, RG, and BRK groups of 8 to 10 animals each. Stress was induced by means of immobilization (being restrained in plastic tubes for 30 min and electroshock (0.5 mA in mice or 2 mA in rats for 5 min). The no-stress group was not exposed to stress. Rats in the RG group received oral doses of 200 mg RG extract/kg body weight daily. The BRK group was fed a 30% BRK diet and exposed to stress. Animals were given supplements for 7 days before being exposed to stress, and then were given supplements for 5 days with exposure to stress. When the stress exposure ended, the animals were observed for stress-related changes in behavior and their plasma corticosterone levels were measured. BRK supplementation was associated with a partial blockade of the effects of stress on locomotion and elevated plus-maze test results in rats and mice. It was also associated with a partial reduction in stress-induced behaviors such as freezing, burrowing, smelling, face-washing, and rearing. BRK supplementation did not have a significant effect on plasma corticosterone levels, which were increased in the animals exposed to stress ($p<0.01$). The mice in the RG group received RG in water (2 mg RG/mL H_2O), and the BRK group received a 30% BRK diet (weight) for 7 days. Both groups were evaluated for signs of fatigue. BRK supplementation increased endurance, as indicated by time on the rota-rod, in cold water, and on the horizontal wire. These results suggest that BRK supplementation partially protects the animal from the effects of stress and may also contribute to resistance to fatigue on physical exertion.

Key words: stress, fatigue, *koji*, behavioral activity, corticosterone

Introduction

Stress is the combination of reactions to various types of stimuli that arise as the body attempts to maintaining biochemical homeostasis in the face of those stimuli (1-4). In humans, excessive stress may contribute to the development of heart disease (5), high blood pressure (6), and emotional disorders, including depression (7). Research has indicated that more than 60% of diseases is related to stress, especially potentially fatal forms of cardiovascular disease and hypertension, cancer, and gastrointestinal tract disorders (2, 8-10). Stress has also been postulated to be involved with the pathogenesis of a variety of disease states, such as diabetes, immunosuppression, sexual disorders, reproductive dysfunction (10, 11), and such behavioral disorders as anxiety (7, 12). The underlying mechanism may involve the central nervous system (CNS) and the endocrine system, as well as various metabolic pathways (9, 11). The resultant disturbances may vary with the type, intensity, and duration of a particular stressor and the strain it places on the individual (13, 14).

Several natural products have been used to gain relief from depression, anxiety, and sleep disorders, as well as to treat short-term memory loss, hearing loss, inattention, cerebrovascular disorders, high blood pressure, malignancy, and sexual disorders associated with stress (16, 20-22); these products include ginseng (15, 18), artichoke (19), docosahexanoic acid (DHA) (20), and ginko biloba (21). However, it has not been proven that these products can cure stress-induced disorders, nor has it been confirmed that there is a relationship between excessive stress and nutrition.

We have attempted to develop methods of evaluating dietary supplements for their ability to block the effects of stress. In doing so, we selected simple methods of inducing excessive psychological or physiological stress in animals-electroshock and physical and detecting evidence of the effects of such stress. In previous studies conducted in our laboratory (19), we evaluated these methods of inducing stress by monitoring the animals for changes in behavior, and body organ weights. Because many reports show that stress alters corticosterone secretion and IL-2 production (13, 17-23), we also measured these variables in our lab.

Brown rice *Koji* (BRK)-which is prepared using brown rice, wheat, soybeans, glucose, and the fungus *Aspergillus oryzae* has been touted as a "health food," with users assuming it has beneficial enzymatic activity. Fermented brown rice, rice bran, and BRK were introduced as nutritional supplements to prevent the development of diseases associated with aging or as adjuncts to therapy for individuals with compromised immune function, hypertension, cancer, fatigue-related disorders, or liver disorders. Its

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effects have been investigated (24-28), but the mechanism of action and the active ingredient are not yet known. We tested the potential of BRK as a stress- and fatigue-reducing supplement. The primary objective of our study is to determine whether a BRK-supplemented diet can reduce the response to stress in rats and mice compared with ginseng, which is known to have stress-reducing qualities.

Materials and Methods

Animals and diets Male Sprague-Dawley rats (age: 8-10 wk) and male ICR mice (weight: 20-25 g, age: 5 wk) (Hanlim Experimental Animal Co., Yongin, Korea) were used in this study. BRK (Come and See Inc., Incheon, Korea) and red ginseng (RG) extract (Korean Ginseng Inc., Seoul, Korea) used in this study were purchased. RG was used as a positive control with its stress-reducing activity in animals. BRK was prepared using the aleurone of brown rice, embryo of wheat, soybeans and glucose, mixed at a ratio of 65.0:13.0:8.0:7.5:1.5, respectively, and heated by steaming for 50 minutes. This mixture was incubated with *A. oryzae* (1/19 of the total dry weight of the mixture) at 35°C for 48 hr and then dried at room temperature. When the mixture was dry, 1.5% of flavoring materials was added. An analysis revealed that 100 g of BRK contained 14.8 g of crude fat, 19 g of crude protein, 55.1 g of carbohydrates, and trace amounts of other nutrients. Commercial mouse and rat chow was supplied by the Super Feed Co. (Kangwon, Korea). The chow was pulverized and mixed with BRK powder in a gram ratio of 7 : 3. The mixed powder was pelletized at room temperature, and the pellets were used for 14 days thereafter. All of the animals were housed in a controlled environment (temp: 22±2°C; humidity: 55±5%; and a 12-hr/12-hr [6 AM-6 PM] light/dark schedule) and allowed to feed and drink *ad libitum* throughout the experiment. After being acclimated to their environment for 1 week, the animals were divided into 4 groups: 1) no-stress group; 2) stress/control group (S) for rats (after given saline 1 mL/100 g body weight orally) and mice (after given potable water); 3) stress-RG group (S+RG) for rats (after given 200 mg RG/kg body weight/once daily) and for mice (after given 2 mg RG/mL water); 4) stress-BRK group (S+BRK) for rats and mice (after fed 30% BRK diet (weight)). They were given the supplement for a total of 12 days: 7 days without stress, and 5 days with stress.

Induction of stress Stress was induced by restraining the animals. The mice were restrained in well-ventilated conical plastic tubes (diameter: 3 cm; length: 7 cm) for 30 min each day. During this period, they did not have access to food or water. At the end of each restraining period, they were exposed to electroshock at an intensity of 0.5 mA (1-sec duration; 20-sec inter-shock interval) for 5 min (19). Similarly, the rats were restrained in well-ventilated conical polypropylene tubes (diameter: 6.2 cm; length: 16.5 cm) for 30 min each day, and during the restraining period, they did not have access to food or water. At the end of each restraining period, the rats were exposed to electroshock at an intensity of 2 mA (1-sec duration; 20-sec inter-shock interval) for 5 min (19).

Behavioral apparatus After the stress-inducing activity was complete, the animals were monitored through a computer located outside the animal room for evidence of changes in behavior using a computerized EthoVision system (Noldus IT bv, Netherlands). During the locomotor activity and elevated plus-maze tests, behavioral parameters were analyzed using an automatic video tracking system.

Locomotor activity The apparatus used to evaluate changes in locomotor activity due to stress consisted of 9 black plastic boxes (47×47 cm), and the field was bordered by 42 cm high side walls. The total distance covered by each animal in this field and the total time involved in movement were monitored for 20 min after the stress-inducing activity ended (19, 29).

Elevated plus maze test Stress-related changes in the animals' maze-exploring skills were evaluated in an elevated plus-maze box. The box and its 'arms' (interior walls) were made of plastic. The apparatus consisted of 2 'open arms' (interior walls forming areas with a separate entrance and exit) measuring 50×10 cm for rats and 30×6 cm for mice and alternating at right angles with 2 'closed arms' (interior walls with a single entrance but no separate exit) enclosed by high walls (30 cm for rats and 20 cm for mice). The 4 arms delineated a central area of 10×10 cm. The whole apparatus was placed 50 cm above the floor. Animals were placed in the central square after undergoing stress and were allowed to explore the maze freely for 5 min. The investigators measured the time each animal spent in open versus closed arms of the maze (19, 29).

Stress-related activity tests After the stress-inducing activity ended, each animal was placed in an individual plastic cage (40×20×18 cm for rats; 26×20×13 cm for mice). Their behavioral activities were evaluated soon thereafter. The time spent smelling, feeding, burrowing, freezing, tailing, face washing and grooming time were recorded over a 5-min period, (19, 20); rearing frequency was measured using the EthoVision system for 20 min thereafter (19, 29).

Blood sampling and measurement of plasma corticosterone levels After their locomotor activity was monitored, the animals were sacrificed. The investigators then drew blood samples (rats: 4 mL each; mice: 1.5 mL each) in heparinized tubes directly from the heart between 10:00 AM 2:00 PM, and the adrenal gland in rats and spleen in mice were then dissected and weighed.

Serum corticosterone levels were measured (17, 19) using a high-performance liquid chromatography (HPLC) system consisting of an SI-2 3001 pump, an SI-2 3002 UV-visible detector, an SI-2 3004 column oven (Shiseido, Tokyo, Japan), and a column Capacell Pak C18 MG 120 (5 μm, 3×250 mm). Corticosterone and dexamethasone (Sigma, St. Louis, MO, USA) were used as an internal standard. Standard solution (40 μL) was injected into the HPLC column and used a solution consisting of acetonitrile, methanol, and 0.03% sulfuric acid solution at a ratio of 32:4:64, respectively, as the mobile phase with a flow rate of 500 μL/min. Corticosterone levels were determined at an absorbance wavelength of 240 nm using a dsCHROM computing program (Shiseido, Tokyo, Japan).

Resistance to physiological stress At the end of the 7-day supplemental diet period, the ability of the animals to withstand physiological stress was evaluated using the horizontal wire test, rota-rod test, and swimming test. Using a slightly modified version of the horizontal wire test described by Hui *et al.* (30), we lifted each mouse by its tail and allowed it to grasp a horizontal wire (diameter: 5 mm; length: 150 cm) located 80 cm above the table with its forepaws and then its tail. The time spent balancing on the horizontal wire was monitored using a stop watch and recorded. Each animal was also placed inside a rota-rod spinning at a speed of 60 rpm. The mice were allowed to run in the rota-rod until they were exhausted to the point of dropping from the rod (31), and the total running time was recorded. The mice were then placed in a circular stainless steel water tank (diameter: 150 cm; height: 50 cm) filled with water to a depth of 15 cm 5 at a time and forced to swim in water maintained at a temperature of 8±2°C, (18, 25, 31). The mice were allowed to swim until exhausted to the point of drowning. The time spent in swimming was monitored using a stop watch and recorded.

Statistical analysis Data are expressed as the mean± SEM. An analysis of variance was used to compare the scores among the groups for each variable. This was followed by post hoc comparisons using the Newman-Keuls test.

Results and Discussion

Effects of BRK on locomotor activity The total movement time and distance covered by the animals during the locomotor activity test were significantly different between animals exposed to stress and those that were not exposed (Fig. 1). Both mice and rats exposed to stress spent significantly less time moving and covered a significantly shorter distances. In animals that received a BRK supplement, however, locomotor activity in stressed animals not suppressed to the same degree as in non-supplemented animals. The decline in locomotor activity observed with BRK supplementation was similar to that seen with ginseng supplementation.

Effects of BRK on specific stress-related behaviors As shown in Fig. 2 and 3, animals exposed to stress spent a significantly longer period of time during the 10-min observation period engaged tin freezing, grooming, face-washing, and burrowing behaviors, but less time engaged in smelling behaviors during that time period and in rearing during the 20 min that were set aside to observe this behavior. These results are similar to those reported by Takeuchi (20). These stress-induced behaviors were reduced during BRK supplementation in rats (i.e. less times was spent engaged in freezing, burrowing, grooming, and face-washing) and in mice (i.e. less time was spent engaged freezing, burrowing, grooming, and rearing). Although there were some differences in the amount of time spent face-washing, freezing, and smelling, most of these effects were similar to those seen in animals that received ginseng.

Effects of BRK on exploratory activity in the elevated plus maze The animals that had been exposed to stress spent a significantly longer amount of time in the open versus closed arms of the maze ($p<0.01$) during the 10-

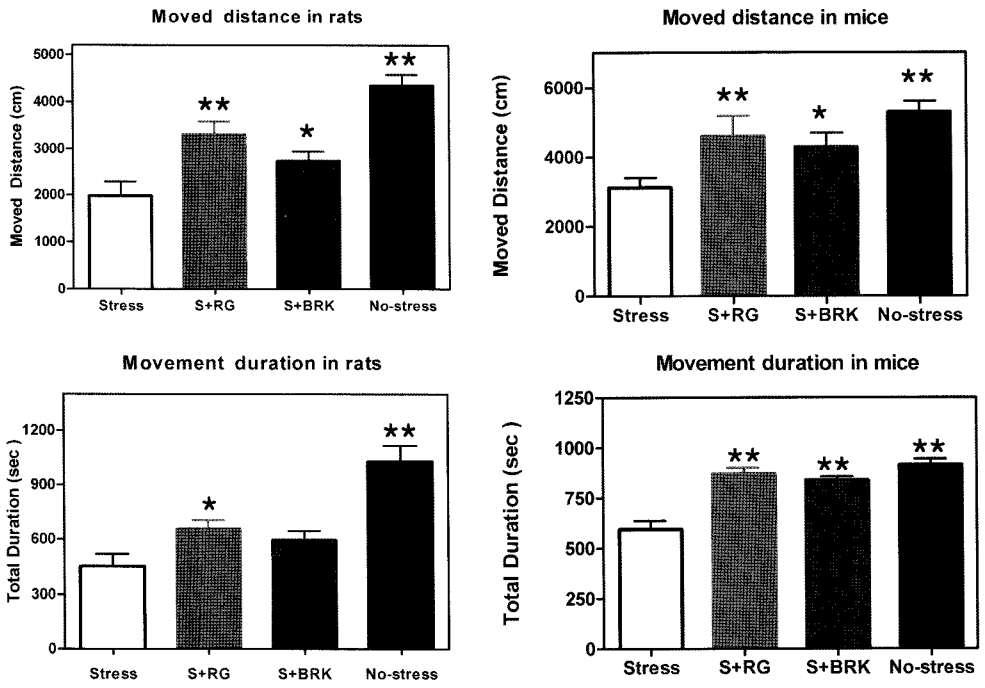

Fig. 1. Effects of BRK on locomotor activity in rats and mice (n=9). Each bar represents the mean ± SE of the distance moved and movement duration during the 20-min observation period after loading stress. No-stress, S + RG (RG 200 mg/kg or RG 2 mg/mL containing water + stress) or S + BRK (30% BRK diet + stress), versus stress group (saline or potable water + stress), $^{**}p<0.01$; $^{*}p<0.05$.

min observation period compared with those that had not been exposed to stress (Fig. 4); this finding is similar to that of other studies (36, 20). This response was significantly reversed in animals that had received BRK supplementation ($p<0.05$); a similar effect was also seen in animals that had received ginseng.

Effects of BRK on plasma corticosterone levels and organ weight As shown in Fig. 5 and 6, the wet weight of adrenal glands removed from rats that had been exposed to stress was significantly increased ($p<0.01$). Additionally, these animals had higher corticosterone levels than those that had not been exposed to stress. It is well known that environmental stress leads to grooming and face washing and that corticotropin-releasing hormone (CRH) may be involved in this reaction (34). In some studies, these responses to stress (specifically to an electrical stimulus) have been accompanied by an increase in blood pressure and heart rate (35). Stress has been thought to induce a nonspecific response involving the release of adrenal glucocorticoid and catecholamines (37-40). The hypothalamic-pituitary-adrenal (HPA) axis has traditionally been regarded as the system responsible for mediating this response (2, 13, 17, 33). HPA activity is influenced mainly by medial parvocellular neurons in the paraventricular nucleus of the hypothalamus, which secrete primarily CRH and vasopressin; in turn, these hormones act synergistically to stimulate the secretion of adenocorticotropic hormone (ACTH) by corticotropic cells in the pituitary gland (11, 13, 33, 40, 41). ACTH enters the

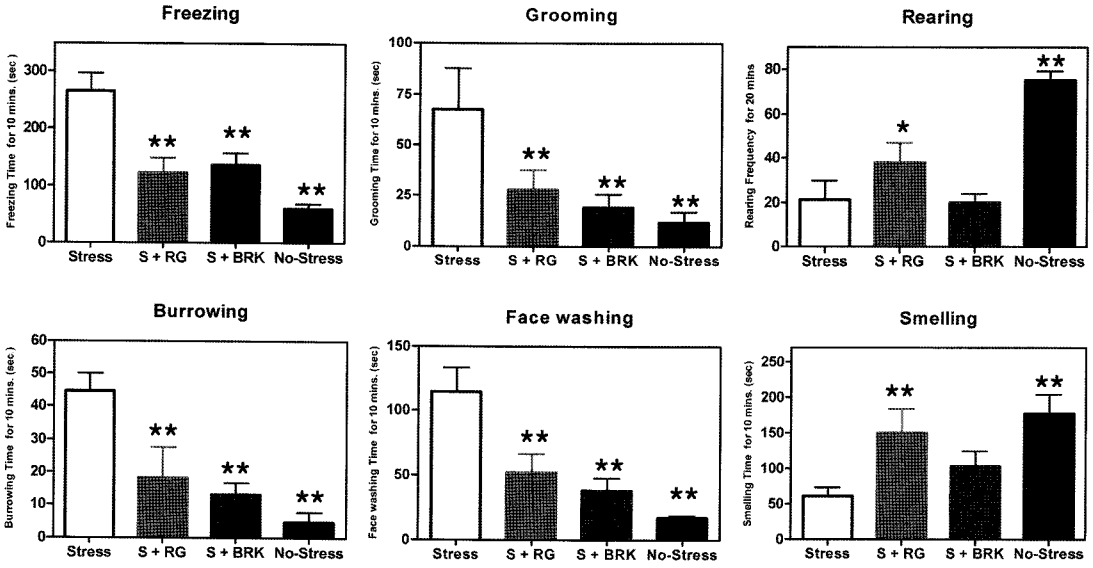

Fig. 2. Effects of BRK on stress-related behaviors in rats (n=9). Each bar represents mean±SE of the total activity time during the 5-min observation period and rearing frequency during a 20-min observation period after loading stress. $^{**}p<0.01$; $^{*}p<0.05$.

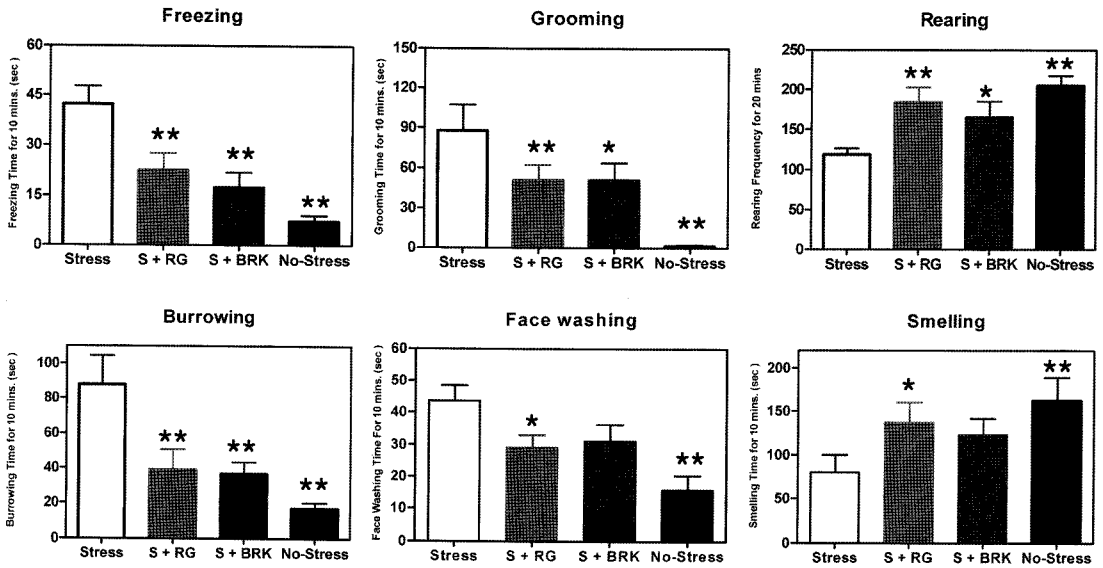

Fig. 3. Effects of BRK on stress-related behaviors in mice (n=9). Each bar represents mean±SE of the total activity time during the 5-min observation period and rearing frequency during the 20-min observation period after loading stress. $^{**}p<0.01$; $^{*}p<0.05$.

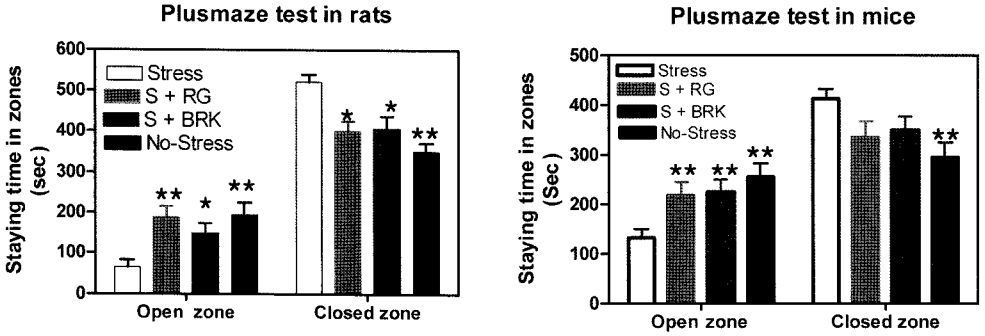

Fig. 4. Effects of BRK on the exploratory activity in the elevated plus maze in rats and mice (n=9). Each bar represents mean±SE of the time spent on the open and closed arms. $^{**}p<0.01$; $^{*}p<0.05$.

systemic circulation and stimulates the synthesis and release of corticosterone from the adrenal glands (40). Under stressful conditions, ACTH levels rise (40, 43), the rate at which corticosterone is released from the adrenals increases, and adrenal hypertrophy takes place (17, 19, 40, 42, 43). Consistent with the findings in a number of other studies (17, 40), we found that exposure to various kinds of stressors induces a clear increase in corticosterone secretion. We also found that the stress-induced increase in plasma corticosterone levels and overgrowth of the adrenal glands were attenuated in animals that received ginseng or BRK; however, the difference in corticosterone levels and adrenal gland size was significant between non-supplemented animals and ginseng-supplemented animals ($p<0.01$), but not between non-supplemented animals and BRK-supplemented animals.

Stress was also associated with a reduction in spleen size in both rats and mice. This reduction in spleen size was reversed in animals that received BRK or ginseng. The stress-related change in spleen size may have been evidence of a change in immune function. Stimulation of the immune system induces a proliferation of immune cells in the spleen and the production of cytokines (44). It is known that glucocorticoids have immunoregulatory activities resulting in a broad spectrum of cellular immune responses (37). In addition, there is evidence suggesting a

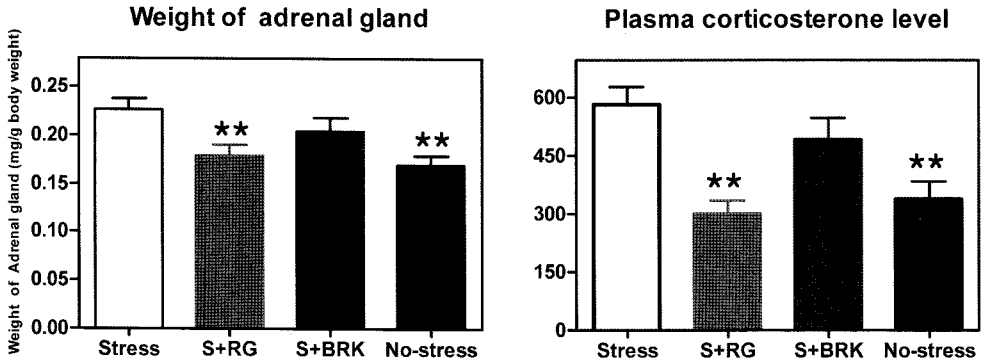

Fig. 5. Effects of BRK on plasma corticosterone levels and wet weight of adrenal glands in rats (n=9). Each bar represents mean± SE of wet weights of adrenal glands and plasma corticosterone levels after loading stress. $^{**}p<0.01$; $^{*}p<0.05$.

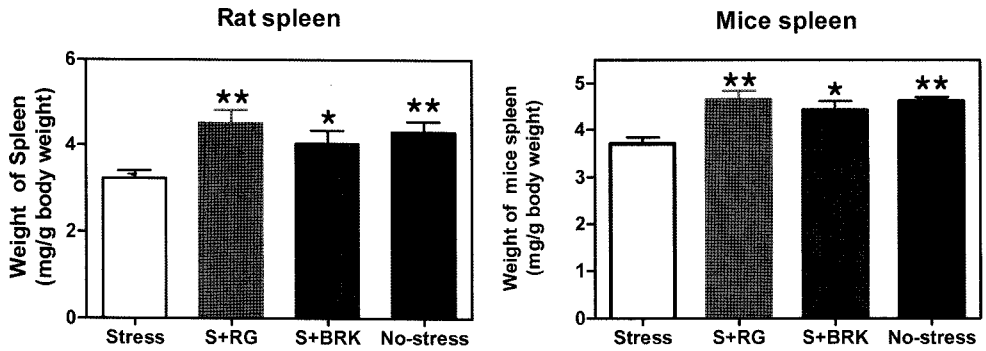

Fig. 6. Effects of BRK on wet weight of spleen in rats and mice (n=9). Each bar represents mean ± SE of wet weights of spleens after loading stress. $^{**}p<0.01$; $^{*}p<0.05$.

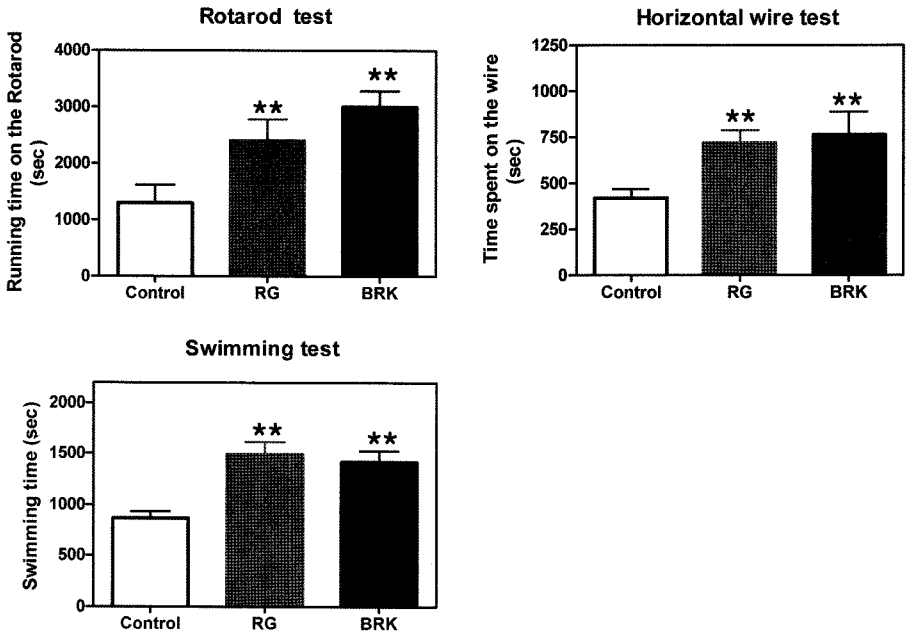

Fig. 7. Effects of BRK on resistant activities to physical stress in mice. Each bar represents mean±SE of endurance time on the rota-rod or the horizontal wire, or in the swimming pool. Mice were given water containing RG (2 mg/mL H_2O), a 30% FRK diet (weight), or potable water for 7 days and were exposed to physical stress. $^{**}p<0.01$; $^{*}p<0.05$.

"hard-wired" interactive relationship between the CNS and the immune system, as indicated by the observation that nerve endings are in direct contact with T lymphocytes in the spleen in rats (45). Based on these observations, we can suggest 2 mechanisms that may be responsible for spleen shrinkage under stress. The first one is a hormone-related mechanism, namely, stress-induced elevation of glucocorticoid levels that suppresses cellular immunity. The second one is a result of the CNS directly inhibiting immune function through its innervation of the spleen.

Effects of BRK on resistance to physiological stress The effect of BRK on the response to physiological stress was evaluated using the horizontal wire test, cold swimming test, and rota-rod test. Specifically, motor coordination and endurance were evaluated using these tests. As shown in Fig. 7, animals that received BRK demonstrated a significantly prolonged swimming time, balancing time on the horizontal wire, and running time on the rota-rod compared with animals that did not receive such supplementation ($p<0.01$); these outcomes were similar to those observed in animals that received ginseng. These results suggest that BRK enhances physical capacity during stress or blocks certain responses to stress.

In this study, we found that animals exposed to stress exhibit changes in locomotor activity behavior, exploratory (maze) activity, plasma corticosterone levels, and body organ weight. These responses were similar to those observed in our earlier studies (19) as well as in the studies of other investigators (15, 17-20, 40, 42, 45). We also found that all of these responses were attenuated in animals that received BRK supplementation, except the change in adrenal function. BRK-which was prepared with brown rice, wheat, soybean, glucose, and *A. oryzae*-has been used as a health food, because its enzymatic activity is believed to enhance human health. It is regarded as highly nutritious because of it provides dietary fiber, protein, and essential amino acids, and several vitamins. BRK and similar products (e.g. fermented brown rice or rice bran) were introduced as nutritional products to enhance good health and stamina, as dietary supplements to prevent adult diseases, or as adjuncts to therapy for various diseases in adults (24-28). In our study, the effects of BRK on the response to electroshock and restraint stress were similar to or weaker than the effects of ginseng. However, it did demonstrate prominent effects on resistance to the changes induced by physiological stress (swimming, rotarod, and wire test). We propose that the anti-stress effects of BRK are not caused by a direct effect on the CNS or endocrine system, but by indirect effects that result in an enhancement of physical capacity or stamina.

BRK attenuates the response to stress in experimental animals through indirect physiological effects, resulting in an overall effect of improved stamina. Thus, it has the potential to be used as a functional food product for alleviating stress.

Acknowledgments

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References

1. Selye H. Stress without distress. WW Lippincott Co., Philadelphia, PA, USA. p. 31 (1974)
2. Chrousos GP, Gold PW. The concepts of stress and stress system disorders: Overview of physical and behavioral homeostasis. JAMA 267: 1244-1252 (1992)
3. Selye H. The Stress of life. McGraw-Hill Book Co., New York, NY, USA. pp. 62-63 (1978)

4. Selye H. History of the Stress concept. pp. 7-36. In: Handbook of Stress, Goldberg L, Brenitz S (eds). The Free Press, New York, NY, USA (1993)
5. Kamarck T, Jennings JR. Biobehavioral factors in cardiac death. Psychol. Bull. 109: 42-75 (1991)
6. Snider SR, Kuchel O. Dopamine: an important neurohormone of the symphatoadrenal system. significance of increased peripheral dopamine release for the human stress response and hypertension. Endocr. Rev. 4: 291-309 (1983)
7. Kessler RC. The effects of stressful life events on depression. Annu. Rev. Psychol. 48: 191-214 (1997)
8. McCain NL, Smith, JC. Stress and coping in the context of psychoneuroimmunology: A holistic framework for nursing practice. Arch. Psychiatr. Nurs. 814: 221-227 (1994)
9. Brier A, Albus M, Picker D, Zahn TP, Wolkowitz OM, Paul SM. Controllable and uncontrollable stress in humans: Alterations in mood and neuroendocrine and psychophysiological function. Am. J. Psychiat. 144: 11-19 (1987)
10. Hurst MW, Jenkins CD, Rose RM. The relation of psychological stress to onset of medical illness. Ann. Rev. Med. 27: 301-312 (1976)
11. Staratakis CA, Chrousos GP. Neuroendocrinology and pathophysiology of the stress system. Ann. NY. Acad. Sci. 771: 1-18 (1995)
12. Blazer D, Hughes D, George LK. Stress life events and the onset of a generalized anxiety syndrome. Am. J. Psychiat. 144: 9-18 (1987)
13. Kioukia-Fougia, N, Antoniou K, Bekris S, Liapi C, Christofidis I, Papadopoulou-Diafoti Z. The effects of stress exposure on hypothalamic-pituitary-adrenal axis, thymus, thyroid hormones and glucose levels. Neuropharmacol. Biol. Psychiatry 26: 823-830 (2002)
14. Dimsdale E, Keefe HJ, Stein MB. Stress and psychiatry. Vol 2, pp.7-36. In: Comprehensive textbook of psychiatry. Sadock BJ, Sadock VA (eds). WW Lippincott Co., Philadelphia, PA, USA (2000)
15. Takahashi M, Tokuyama S, Kaneto H. Anti-stress effect of ginseng on the inhibition of the development of morphine tolerance in stressed mice. Jpn. J. Pharmacol. 59: 399-404 (1992)
16. Kaneko H, Nakanishi K, Murakami A, Kaidoh H, Kuwashima K. The acute effects of massive dose of red ginseng on healthy adults under the condition of cold stress. Ginseng Rev. 22: 20-24 (1996)
17. Kim DH, Jung JS, Moon YS, Sung JH, Suh HW, Kim, YH, Song DK. Inhibition of intracerbroventricular injection stress-induced plasma corticosterone levels by intracerebroventricularly administered compound K, a ginseng saponin metabolite, in mice. Biol. Pharm. Bull. 26: 1035-1038 (2003)
18. Choi SS, Lee JK, Suh HW. Effect of ginsenosides administered intrathecally on the antinocieption induced by cold water swimming stress in the mouse. Biol. Pharm. Bull. 26: 858-861 (2003)
19. Tan-Lee BS, Yu GY, Kim K, Han H, Han J, Lee GS, Kim ES, Lee CJ, Ryu JH, Cheong JH. Anti-stress effect of Artichoke juice in SD rats and ICR mice. Food Sci. Biotechnol. 13: 302-308 (2004)
20. Takeuchi T, Iwanaga M, Harada E. Possible regulatory mechanism of DHA-induced anti-stress reaction in rats. Brain Res. 964: 136-143 (2003)
21. Ward CP, Rsdd K, Williams BM, Caler JR, Luo Y, McCoy JG. Ginkgo bioloba extract: Cognitive enhancer or anti-stress buffer. Pharmacol. Boichem. Be. 72: 913-922 (2002)
22. Ai AL, Bolling SF. The use of complementary and alternative therapies among middle-aged and older cardiac patients. Am. J. Med. Qual. 17: 21-27 (2002)
23. Glaser R, Kennedy S, Lafuse WP, Bonneau RH, Speicher C, Hillhouse J, Kiecolt-Glaser JK. Psychological stress-induced modulation of interleukin 2 receptor gene expression and interleukin 2 production in peripheral blood leukocytes. Arch. Gen. Psychiat. 47: 707-712 (1990)
24. Choi, YS, Jang, JH. Effects of rice bran and wheat bran on the levels of lipids in plasma, liver and feces, and short-chain fatty acids in large bowel of rats. Food Sci. Biotechnol. 10: 166-171 (2001)
25. Kim KM, Yu KW, Kang DH, Koh JH, Hong BS, Suh HJ. Anti-stress and anti-fatigue effects of fermented rice bran. Biosci. Biotechnol. Biochem. 65: 2294-2296 (2001)
26. Jeon TI, Hwang SG, Lim BO, Park DK. Extracts of Phellinus linteus grown on germinated brown rice suppress liver damage induced by carbon tetrachloride in rats. Biotechnol. Lett. 25: 2093-2096 (2003)
27. Lim BO, Yamada K, Cho BG, Jeon T, Hwang SG, Park T, Kang SA, Park DK. Comparative study on the modulation of IgE and cytokine production by Phellinus linteus grown on germinated brown Rice, Phellinus Linteus and germinated brown rice in murine splenocytes. Biosci. Biotechnol. Biochem. 68: 2391-2394 (2004)
28. Choi HD, Park YK, Kim YS, Chung CH, Park YD. Engineering/ Processing/ Sensory Evaluation : Effect of pretreatment conditions on γ-aminobutyric acid content of brown rice and germinated brown rice. Korean J. Food Sci. Technol. 36: 761-764 (2004)
29. Noldus LPJJ, Spink AJ, Tegelenbosch AJ. EthoVision: A versatile video tracking system for automation of behavioral experiments. Psychonom. Society 33: 398-414 (2001)
30. Hui KM, Huen MS, Wang HY, Zheng H, Sigel E, Baur R, Ren H, Li ZW, Wong JT, Xue H. Anxiolytic effect of wogonin, a benzodiazepine receptor ligand isolated from Scutellaria baicalensis Georgi. Biochem. Pharmacol. 64: 1415-1424 (2002)
31. Lee GS, Tan-Lee BS, Kim M, Dong KU, Kim J, Yu GY, Han J, Ko HS, Park IH, and Cheong JH. Stress related activities of sun-ginseng in SD rats and ICR mice. J. Appl. Pharmacol. 12: 242-249 (2004)
32. Beck CH, Fibiger HC. Conditioned fear-induced changes in behavior and in the expression of the immediate early gene C-fos: with and without diazepam pretreatment. J. Neurosci. 15: 709-720 (1995)
33. Kim DH, Yoo SM, Jung JS, Min SK, Son BK, Suh HW, Song DK. Effects of ginseng saponin administered intraperitoneally on the hypothalamo-pituitary -adrenal axis in mice. Neurosci. Lett. 343: 62-66 (2003)
34. Gispen WH, Isaacson RL. ACTH-induced excessive grooming in the rat. Pharmacol. Ther. 12: 209-246 (1981)
35. Brandao ML, Anseloni VZ, Pandossio JE, De Araujo JE, Castilho VM. Neurochemical mechanisms of the defensive behavior in the dorsal midbrain. Neurosci. Biobehav. Rev. 23: 863-875 (1995)
36. Albonetti ME, Farabollini F. Social stress by repeated defeat: effects on social behaviour and emotionality. Behav. Brain Res. 62: 187-193 (1994)
37. Munck A, Guyre PM, Holbrook NJ. Physiological functions of glucocorticoids in stress and their pharmacological actions. Endocr. Rev. 51: 25-44 (1984)
38. Ida Y, Tanaka M, Tsuda A, Tsujimaru S, Nagasaki N. Attenuating effect of diazepam on stress-induced increases in noradrenaline turnover in specific brain regions of rats: antagonism by Ro 15-1788. Life Sci. 37: 2491-2498 (1985)
39. Finlay JM, Zigmond MJ, Abercrombie ED. Increased dopamine and norepinephrine release in medial prefrontal cortex induced by acute and chronic stress: effects of diazepam. Neuroscience 64: 619-628 (1995)
40. Djordjevic J, Cvijic G, Davidovic V. Different activation of ACTH and corticosterone release in response to various stressors in rats. Physiol. Res. 52: 67-72 (2002)
41. Koob GF, Bloom FE. Corticosterone-releasing factor and behavior. Fed. Proc. 44: 259-263 (1985)
42. Morimoto A, Nakamori T, Morimoto K, Tan N, Mukurami N. The central role of corticotropin-releasing factor (CRF-41) in psychological stress in rats. J. Physiol. 460: 221-229 (1984)
43. Walker C, Perrin M, Vale W, Rivier C. (1986). Ontogeny of the stress response in the rats: role of the pituitary and the hypothalamus. Endocronology 118: 1445-1451 (1986)
44. Cantrell DA, Smith KA. The interleukin 2 T cell system: a new cell growth model. Science 224: 1312-1316 (1984)
45. Felton SY, Olschowka J. Noradrenergic sympathetic innervation of the spleen, II: tyrosine hydroxylase (TH)-positive nerve terminals from synaptic-like contacts on lymphocytes in the splenic white pulp. J. Neurosci. Res. 18: 37-48 (1987)