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Effects of pre-germinated brown rice on depression-like behavior in mice

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Abstract

We investigated the antidepressant-like effects of pre-germinated brown rice (PGBR) and polished rice (PR) pellets, respectively, in comparison with control (AIN-93G) pellets in the forced swimming test and the learned helplessness paradigm in mice. Mice were fed respective pellets for 30 days. The immobility time on the 2nd day of the forced swimming test was shorter in mice fed with PR or PGBR pellets than in mice fed with control pellets. In the learned helplessness paradigm, the number of escape failures in mice fed with PGBR pellets was significantly smaller than that in mice fed with control pellets. Compared to the control group, an increase in serotonin (5-HT) levels, but not in 5-hydroxyindoleacetic acid (5-HIAA) levels, and a decrease in the 5-HIAA/5-HT ratio were observed in the frontal cortex of the PGBR group. There were no differences among the three groups in terms of 5-HT and 5-HIAA levels and their ratios in the hippocampus and striatum. The levels of noradrenaline and 3-methoxy-4-hydroxyphenylglycol were not affected by the food pellets in all the brain regions tested. Additionally, we could not detect any differences in the expression of the 5-HT_{1A} receptor and the 5-HT transporter in the frontal cortex of the three groups. These results suggest that the increase of 5-HT levels in the mouse frontal cortex contributes to the antidepressant-like effects of PGBR pellets.

Keywords: Pre-germinated brown rice; Antidepressant-like effects; Forced swimming test; Learned helplessness paradigm; 5-hydroxytryptophan (5-HT; serotonin)

1. Introduction

Rice grain consists of an endosperm, a bran layer and a germ, and is an important energy source for humans. Polished rice (PR), the staple food of Asians, is produced by eliminating the fiber-rich bran layer from unpolished rice, namely, brown rice (BR). Pre-germinated brown rice (PGBR) is produced by soaking BR in water to induce slight germination. PGBR contains abundant dietary fiber, vitamins and minerals in the bran layer and embryo, and tastes better than BR. It has been reported that PGBR effectively reduced glucose levels in diabetic rats (Hagiwara et al., 2004; Seki et al., 2005). We have reported the effects of PR and PGBR on learning and memory ability in mice that showed no preference for the type of food pellet given (Mamiya et al., 2004). However, the effects of PGBR on other brain functions remain unknown. In this study, we investigated whether PGBR affected the depression-like behavior in mice.

In order to determine the antidepressant-like effects of food pellets in mice, two representative screening methods, the forced swimming test and the learned helplessness paradigm, were used (Cryan and Mombereau, 2004). The finding that immobility in the forced swimming test is sensitive to several antidepressants suggests that this behavior is a form of depression-like response in rats and mice (see reviews: Borsini, 1995; Lucki, 1997; Cryan et al., 2005; Petit-Demouliere et al., 2005). Another animal model of depression, learned helplessness, is used to study the behavioral consequences of exposure to stressful events over which an animal has no control (Weiss et al., 1981). For example, in this paradigm, rats exposed to

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uncontrollable electric shocks show an increase in the number of escape failures on subsequent trials, suggesting that this increase is a sign of a depressive state. This model is highly sensitive to antidepressants (Thiebot et al., 1992; Besson et al., 1999) and to anxiolytics (Martin and Puech, 1996; Maudhuit et al., 1997; Maier and Watkins, 2005), and is being used increasingly to investigate the neurobiology of depressive illness.

According to the monoamine theory, depression is caused by an impairment of serotonergic and/or noradrenergic neurotransmission and the concomitant decrease of the biophase concentrations of these transmitters (Hindmarch, 2001; Wong and Licinio, 2001). Classical and recent antidepressants (e.g., tricyclic reagents, selective serotonin reuptake inhibitors (SSRIs), and selective noradrenaline inhibitors (SNRIs)) regulate serotonin (5-HT) and noradrenaline (NA) levels in the brain. Therefore, we examined whether the levels of NA and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), and 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were changed in the frontal cortex, hippocampus and striatum in mice fed PR and PGBR pellets for 30 days. Furthermore, the expression of the 5-HT_{1A} receptor and the 5-HT transporter was checked by western blot analysis because antidepressants are known to affect their expression (Benmansour et al., 1999; Hensler, 2003).

2. Materials and methods

2.1. Animals

Five-week-old male ICR mice (Nihon SLC Co., Shizuoka, Japan) were purchased and food pellets were adequately given to them. The animals were housed in a controlled environment (23±1 °C, 50±5% humidity) and given access to water *ad libitum*. The room lights were on between 7 h30 and 19 h30. We used standard food pellet (AIN-93G, Oriental Yeast Co., Ltd., Japan) containing cornstarch. The ingredients in the PR or PGBR pellet were the same as those in AIN-93G (control pellets hereafter) except for cornstarch, which was replaced with PR or PGBR powder (Table 1). PR and PGBR were the same type of short grain rice (Japonica) produced in the same area in Hokkaido, Japan. PGBR was prepared at 25–30% water content to induce germination and dried to 15%, in the same manner as PR according to a patented method (Patent No. 3738025, JP, November 4, 2005). Mice given respective food pellets for 30 days were separated into three groups to conduct behavioral and neurochemical tests independently. Desipramine (Sigma) was suspended in 0.3% carboxymethylcellulose and given at a dose of 0.1 ml/10 g body weight. All experiments were performed in accordance with the Guidelines for Animal Experiments of Meijo University and the Guiding Principles for the Care and Use of Laboratory Animals approved by the Japanese Pharmacological Society (1987).

Table 1
Standard ingredients in food pellet

AIN-93G	Constituents (%)
Cornstarch	39.7
Casein	20
L-cystine	0.3
Alpha-cornstarch	13.2
Sucrose	10
Bean oil	7
Cellulose powder	5
Mineral	3.5
Vitamin	1
Choline bicitrates	0.25
Butylhydroquinone	0.0014

AIN-93G: standard food pellet (Oriental Yeast Co. Ltd., Japan). Cornstarch is replaced with PR powder or PGBR powder. Alpha-cornstarch is added to solidify food pellet.

2.2. Behavioral and biochemical tests

2.2.1. Experiment 1: forced swimming test

The forced swimming test employed was essentially similar to that described previously (Matsuno et al., 1996; Chen et al., 2006). We used 12 mice in each group. Briefly, on day 30, mice were dropped individually into transparent glass cylinders (diameter 17 cm, height 50 cm) filled with water (approximately 25 °C) to a depth of approximately 25 cm, and left there for 15 min. In such a situation from which they cannot escape, the mice rapidly became immobile, that is, they floated in an upright position and made only small movements to keep their heads above water. The duration of immobility (immobility time) was measured. Twenty-four hours later, each mouse was dropped into the water again and immobility time was recorded for the last 5 min of the 6-min testing period. Desipramine (20 mg/kg, i.p.) was administered 30 min before measurement on the 2nd day of the forced swimming test.

2.2.2. Locomotor activity

The day after the forced swimming test (day 32), mice were placed individually in transparent acrylic cages (length 26 cm, width 44 cm, height 40 cm). To examine whether the forced swimming affected spontaneous activity, we measured locomotion every 5 min for 60 min using digital counters with infrared sensors placed on the walls (Scanet SV-20, Melquest Co. Ltd., Toyama, Japan) (Noda et al., 1997).

2.2.3. Experiment 2: learned helplessness paradigm

The learned helplessness paradigm was carried out as previously reported (Ukai et al., 2002) using 9 mice in each group. The Plexiglas chamber (length 15 cm, width 18 cm, height 18 cm) has stainless-steel grids spaced 1 cm apart (MED-PC Associates, Inc., USA), and was placed in a soundproof box. On day 30 of feeding (day 0) scrambled inescapable electric footshocks were delivered to the grid floor (0.6 mA, 30 s duration, 30 s interval). In the next 5 days, each animal was subjected to 30 active conditioned avoidance sessions. One avoidance session consisted of a 33 s avoidance duration with a 30 s interval between sessions. During the first 3 s of the avoidance session, a small cue light and a buzzer (85 dB) were presented as conditioned stimulus, and the animal was exposed to the 30 s electric footshock (0.6 mA). To escape from this

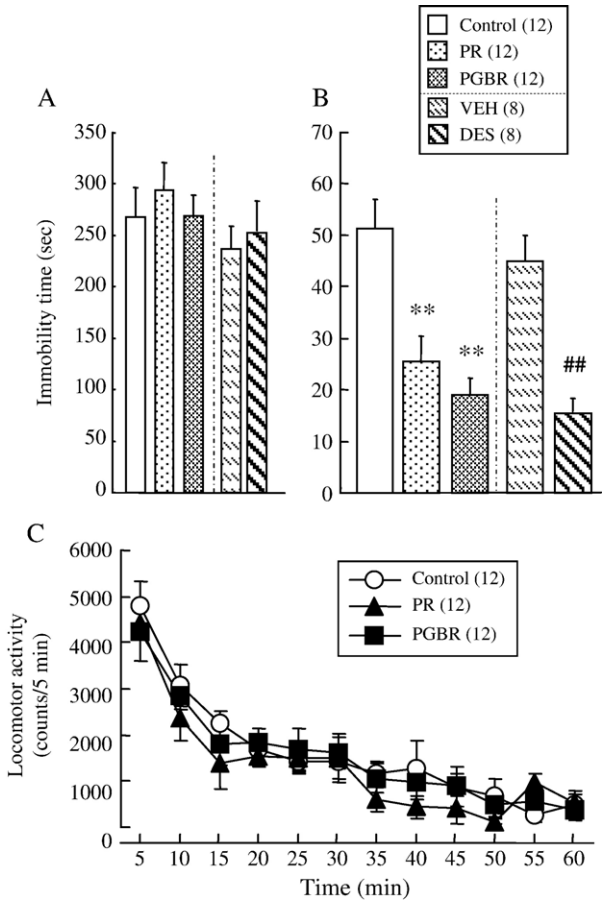

Fig. 1. Effects of three types of food pellets on immobility time in the forced swimming test on the 1st day (A) and 2nd day (B) in mice. Control: AIN-93G pellets, PR: pellets containing polished rice, PGBR: pellets containing pre-germinated brown rice. Each datum represents the mean±SEM. Locomotor activity (C) is measured every 5 min for 60 min. The number of mice used is shown in parentheses. $^{**}P<0.01$ vs. Control (Tukey's test).

electric footshock, the mouse had to press the lever in the box. The failure of the mouse to escape from the footshock was considered to be an escape failure and the number of those was recorded. Desipramine (20 mg/kg, i.p.) or saline was administered 30 min before measurement for 5 days.

2.2.4. Nociceptive test

Before the learned helplessness paradigm, we examined the sensitivity of mice to electric footshock. In the electric footshock test, we used a transparent acrylic rectangular cage (length 23 cm, width 28 cm, height 12 cm) equipped with a metal wire floor. The shock intensity was increased stepwise manually from 0.1 to 2.0 mA in 0.1 mA increments (20 s interval) until a flinch was observed (Shockgenerator, Neuroscience Idea, Co. Ltd., Osaka, Japan) as our previous report (Mamiya et al., 1998).

2.2.5. Experiment 3: Levels of noradrenaline (NA) and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), and serotonin (5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA)

On day 31, 22 mice (control: $n=7$, PR: $n=7$, PGBR: $n=8$) were sacrificed by focused microwave irradiation for 1.4 s at 5 kW. The brains were quickly removed and the frontal cortex, striatum, and hippocampus were dissected out on an ice-cold glass plate as in previous reports (Noda et al., 1997; Mamiya et al., 1998). Each section was rapidly frozen and stored in a deep freezer at −80 °C until assayed. The levels of monoamines and their metabolites were determined with an HPLC system equipped with an electrochemical detector (HTEC-500, Eicom, Kyoto, Japan). Briefly, each frozen brain sample was weighed and homogenized with an ultrasonic processor in 350 µl of 0.2 M perchloric acid containing isoproterenol as an internal standard. The homogenates were placed on ice for 30 min and centrifuged at 20,000 ×*g* for 15 min at 4 °C. The supernatants were mixed with 1 M sodium acetate to adjust the pH to 3 and injected into the HPLC system equipped with a reversed-phase ODS column (Eicompak MA-5 ODS; 4.6×150 mm; Eicom) and the electrochemical detector. The column temperature was maintained at 25 °C, and the detector potential was set at +750 mV. The mobile phase was 0.1 M citric acid and 0.1 M sodium acetate, pH 3.6, containing 17% methanol, 180 mg/l sodium-L-octanesulfonate, and 5 mg/l EDTA, and the flow rate was set at 500 µl/min.

2.2.6. Experiment 4: expression of 5-HT_{1A} receptor and 5-HT transporter

On day 31, 12 mice (4 mice in each group) were sacrificed by decapitation, the brains were quickly removed, and the frontal cortex, striatum, and hippocampus were dissected out on an ice-

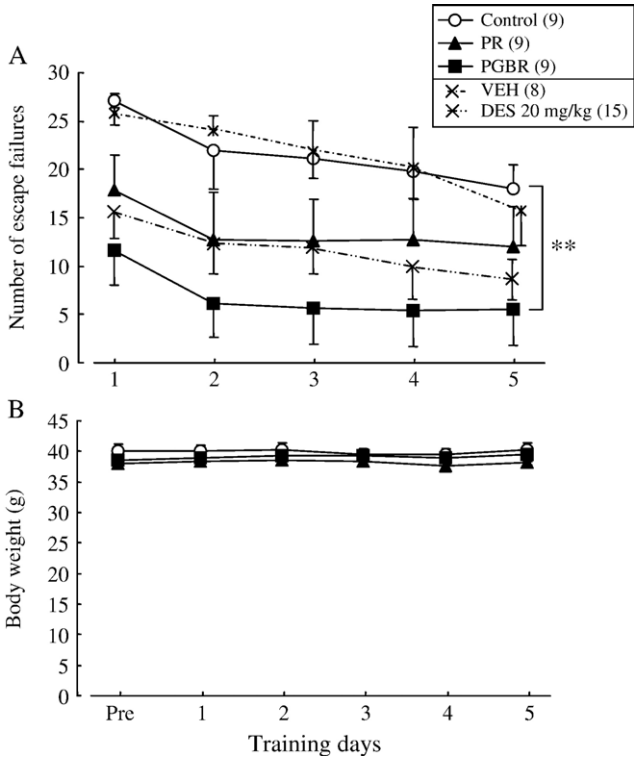

Fig. 2. Effects of three types of food pellets on the number of escape failures in learned helplessness paradigm. Time course of escape failures in learned helplessness paradigm (A). Changes in body weight during learned helplessness test (B). Control: AIN-93G pellets, PR: pellets containing polished rice, PGBR: pellets containing pre-germinated brown rice. Each datum represents the mean± SEM. The number of mice used is shown in parenthesis. $^{**}P<0.01$ vs. Control (Tukey's test).

Table 2
Levels of 5-HT and 5-HIAA, and 5-HIAA/5-HT ratio in the hippocampus and striatum of mice fed three types of food pellets

Food pellet	N	Frontal cortex			Hippocampus			Striatum		
		NA	MHPG	MHPG/NA ratio	NA	MHPG	MHPG/NA ratio	NA	MHPG	MHPG/NA ratio
Control	7	1218.7±132.2	181±16.9	0.151±0.01	1362.4±35.2	198.5±12.4	0.146±0.02	571±102.8	153.0±26.7	0.27±0.06
PR	7	1521.1±77.9	237.3±19.3	0.156±0.02	1464.9±103.8	250.8±27.0	0.168±0.01	515.0±53.3	188.7±38.7	0.36±0.06
PGBR	8	1660.5±140.9	212.1±18.7	0.130±0.02	1577.9±114.7	227.7±23.4	0.144±0.01	508.7±75.0	138.3±24.7	0.29±0.05

The levels of 5-HT and 5-HIAA were determined with an HPLC system equipped with an electrochemical detector. 5-HT, 5-HIAA: ng/g wet tissue. Control: AIN-93G pellets, PR: pellets containing polished rice, PGBR: pellets containing pre-germinated brown rice. Each value represents the mean±SEM. *N* means the number of animals tested. No significant differences were detected.

cold glass plate. Dissected brain tissue was sonicated in RIPA buffer (4 ml buffer/g tissue) containing 1×PBS, 1% Igepal CA-630, 0.5% sodium deoxycholate, and 0.1% sodium dodecyl sulfate (SDS) and proteinase inhibitors (0.1 mg/ml PMSF, 2 μg/ml aprotinin, and 1 mM sodium orthovanadate). The homogenate was placed on ice for 30 min with intermittent shaking, and centrifuged at 12,000 rpm (11,228 ×*g*) for 15 min. The supernatant was collected and centrifuged again, as above. The final resultant supernatant was stored at −70 °C until use. Protein content of the supernatant was determined by the Lowry method. The supernatants containing 50 μg of protein were electrophoresed on 10% SDS-polyacrylamide gel (Bio-Rad) and transferred to PVDF membranes (Millipore). The membranes were incubated with a 1:1000 dilution of 5-HT_{1A} receptor or 5-HT transporter polyclonal antibody (Chemicon) overnight at 4 °C. The membranes were washed with TBST buffer (10 mM Tris-HCl, 150 mM NaCl, 0.1% Tween 20, pH 7.4) and subsequently incubated with goat anti-rabbit horseradish peroxidase-conjugated secondary antibody for 4 h at room temperature. The immune complexes were detected by chemiluminescence (ECL, Pharmacia Biotech) and exposed to X-ray film (Mamiya et al., 2003). The band intensities of the film were analyzed by densitometry (Atto Co. Ltd., Tokyo, Japan).

2.3. Data analysis

All results were expressed as means±SEM for each group. The data of locomotor activity (Fig. 1C), learned helplessness paradigm (Fig. 2A), and body weight (Fig. 2B) were analyzed using repeated measures one-way ANOVA, followed by Tukey's multiple comparison test. Other data were analyzed by one-way ANOVA, followed by Tukey's test. The level of significant difference was taken at $P<0.05$.

3. Results

3.1. Immobility time in forced swimming test and locomotor activity

As shown in Fig. 1A, there was no difference in immobility time among the three groups on the 1st day ($F_{2,\ 35}=0.329$, $P=0.72$). On the 2nd day, mice fed PR and PGBR pellets showed reduced immobility time in comparison with mice fed control pellets ($F_{2,\ 35}=12.98$, $P<0.01$; Fig. 1B). No significant differences in locomotor activity were detected among the three groups ($F_{2,\ 431}=2.49$, $P=0.09$; Fig. 1C).

3.2. Number of escape failures in learned helplessness paradigm

Prior to the learned helplessness test, we examined the sensitivity to electric footshock. Mice fed the three types of food pellets showed similar sensitivity to electric footshock (control: 0.41±0.07, PR: 0.45±0.11, PGBR: 0.40±0.05 mA; $F_{2,\ 26}=0.92$, $P=0.11$). From the 1st day to the 5th day, mice fed control pellets showed larger numbers of escape failures than mice fed PR or

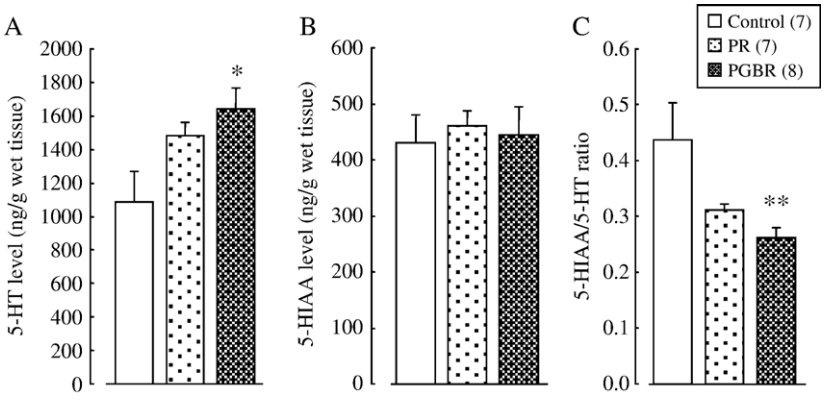

Fig. 3. Levels of 5-HT (A) and 5-HIAA (B) and their ratio (C) in the frontal cortex of mice fed three types of food pellets. Control: AIN-93G pellets, PR: pellets containing polished rice, PGBR: pellets containing pre-germinated brown rice. The levels of 5-HT and 5-HIAA were determined with an HPLC system equipped with an electrochemical detector. Each column represents the mean±SEM. The number of mice used is shown in parenthesis. **$P<0.01$ vs. Control (Tukey's test).

Table 3
Levels of NA and MHPG, and MHPG/NA ratio in the frontal cortex, hippocampus and striatum of mice fed three types of food pellets

Food pellet	N	Hippocampus			Striatum		
		5-HT	5-HIAA	5-HIAA/5-HT ratio	5-HT	5-HIAA	5-HIAA/5-HT ratio
Control	7	1113±72.5	1016.6±62.0	0.92±0.04	1081.1±127.0	780.2±86.5	0.73±0.03
PR	7	1267.4±74.5	1130.0±62.7	0.89±0.03	1203.5±102.4	821.0±59.8	0.69±0.02
PGBR	8	1273.1±40.6	1047.6±72.3	0.82±0.05	1133.4 ±79.5	722.9±46.1	0.64±0.03

The contents of NA and MHPG were determined with an HPLC system equipped with an electrochemical detector. NA, MHPG: ng/g wet tissue. Control: AIN-93G pellets, PR: pellets containing polished rice, PGBR: pellets containing pre-germinated brown rice. Each datum represents the mean±SEM. *N* means the number of animals tested. No significant differences were detected.

PGBR pellets ($F_{2,\ 134}=3.85$, $P=0.035$, Fig. 2A). During the course of the experiment, we noted no marked differences in body weight among the three groups ($F_{2,\ 161}=1.06$, $P=0.36$; Fig. 2B).

3.3. Contents of NA and MHPG, and 5-HT and 5-HIAA in brain

The contents of NA and MHPG in the three brain regions of mice are shown in Table 2. No differences in the contents and their ratios were observed among the three groups. The contents of 5-HT and 5-HIAA in the three brain regions of mice are shown in Fig. 3 and Table 3. Statistical analysis revealed the high content of 5-HT ($F_{2,\ 21}=5.23$, $P=0.015$; Fig. 3A) and the low 5-HIAA/5-HT ratio ($F_{2,\ 21}=6.04$, $P=0.009$; Fig. 3C) in the frontal cortex of mice fed PGBR pellets compared to those of mice fed control pellets, whereas the 5-HIAA content was not changed ($F_{2,\ 21}=0.14$, $P=0.87$; Fig. 3B). On the other hand, there were no significant differences in the contents and ratios in the hippocampus and striatum (Table 3).

3.4. Expression of 5-HT$_{1A}$ receptor and 5-HT transporter in frontal cortex

We could not detect any differences in the expression of the 5-HT$_{1A}$ receptor and the 5-HT transporter among the three groups (5-HT$_{1A}$ receptor: $F_{2,\ 11}=0.11$, $P=0.71$, 5-HT transporter: $F_{2,\ 11}=0.56$, $P=0.13$) (Fig. 4).

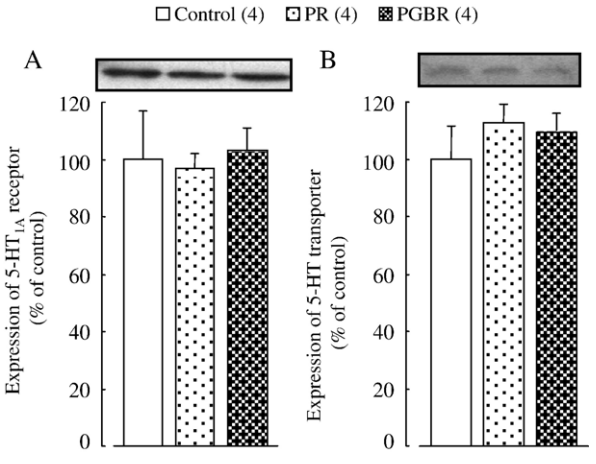

Fig. 4. Expression of 5-HT1A receptor and 5-HT transporter proteins in the frontal cortex of mice. The amount of each protein was determined by western blot analysis using antibodies to 5-HT$_{1A}$ receptor and 5-HT transporter. Each column represents the mean<SEM. The number of mice used is shown in parenthesis.

4. Discussion

In this study, we examined the antidepressant-like effects of PGBR and PR in mice. The three groups of mice showed normal development, similar to our previous report (Mamiya et al., 2004). In the forced swimming test, we demonstrated that mice fed PR and PGBR pellets as well as those administered desipramine (20 mg/kg) showed a significant reduction of immobility time compared with mice fed control pellets on the 2nd day, whereas all four groups showed similar immobility times on the 1st day (Fig. 1A, B). The fact that there were no significant differences in locomotor activity (Fig. 1C) and motor coordination in the rotarod test and in swimming ability in the Morris water maze test (Mamiya et al., 2004) demonstrates that the reduction of immobility time in the forced swimming test is not due to any motor deficits. These results indicate that PR and PGBR may exert antidepressant-like effects in mice. Next, prior to the learned helplessness paradigm, we confirmed that the three food pellet groups showed similar sensitivity to the electric footshock. PGBR but not PR attenuated significantly the number of escape failures from the 1st day to the 5th day compared to control (Fig. 2). The antidepressant-like effect of PGBR appeared to be greater than that of desipramine at 20 mg/kg (Fig. 2A). During the course of the experiment, the body weights of mice in the three groups were not affected by electric footshock and no remarkable physical changes were observed. The learned helplessness behaviors in the laboratory resemble human depression and anxiety (Maier and Watkins, 1998), and in fact, are sensitive to not only antidepressants but also anxiolytics (Martin and Puech, 1996; Maudhuit et al., 1997; Maier and Watkins, 2005). Therefore, it is difficult to separate the effect of antidepressants and anxiolytics in this model. However, considering the results of the two behavioral experiments and the fact that the beneficial effects of PGBR were not observed in 14-day fed mice (data not shown), we suggest that the 30-day feeding of PGBR produces an antidepressant-like effect in mice.

Next, we examined the levels of NA, 5-HT and their metabolites in the frontal cortex, hippocampus and striatum after feeding respective food pellets because it has been reported that the decrease in NA and 5-HT levels is implicated in learned helplessness behaviors, and those behaviors are reversed by antidepressant treatment (Sherman and Petty, 1982). Our three

types of food pellets did not affect NA and MHPG levels in all brain regions tested. It is also proposed that antidepressants work by restoring 5-HT to normal levels, allowing animals to exhibit adaptive responses during an aversive event (Petty et al., 1992; Borsini, 1995). However, we could not observe any differences in the levels of NA, 5-HT and their metabolites in the three brain regions among the three groups except for 5-HT in the frontal cortex. Only in the frontal cortex of mice fed PGBR pellets was 5-HT level significantly increased, and 5-HIAA/5-HT ratio was decreased compared to that of mice fed control pellets. This finding is supported by the report that rats treated with antidepressants demonstrate high levels of 5-HT and less 5-HT turnover in the frontal cortex (Miura et al., 1996). Additionally, we have previously reported that learned helplessness was attenuated by a κ-opioid receptor agonist, U-50,488H, (Ukai et al., 2002) which increases 5-HT efflux from rat cortical neurons (Sbrenna et al., 2000). Furthermore, we tried to detect differences in the expression of the 5-HT_{1A} receptor and the 5-HT transporter by western blot analysis since there are reports that antidepressants, especially SSRIs, might be involved in the regulation of their expression (Benmansour et al., 1999; Hensler, 2003). However, the expression was similar among the three groups. Taken together, it is possible that PGBR may affect 5-HT synthesis in the frontal cortex without changing the expression of the 5-HT_{1A} receptor and the 5-HT transporter.

In conclusion, we have shown that PGBR may have antidepressant-like effects. In future experiments, we will investigate how PGBR and what ingredient in PGBR regulates the 5-HTergic neuronal system in detail.

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