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Effects of high fat diet and bamboo extract supplement on anxiety- and depression-like neurobehaviors in mice

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Abstract

High fat diet is a major causative factor of overweight and obesity, which are associated with increased risk of neuropsychiatric diseases, such as anxiety and depression. In this study, we investigated the protective effects of bamboo extract (BEX) on anxiety- and depression-like neurobehaviors in mice treated with a high fat diet. Male mice with CD-1 genetic background were treated for 2 months with either a standard or a high fat diet (10% or 45% calories from fat, respectively), with or without BEX supplement (11 g dry mass per 17 MJ). The anxiety levels of the mice were evaluated using open field and hole-board tests, and depression was measured using force swimming test. The anxiety responses of the animals were found significantly increased after high fat diet treatment, and this elevation was effectively abolished by BEX supplement. High fat diet seemed to have an anti-depressive effect in the mice at the tested time point, but the effect of BEX supplement on the depression level of the animals was not conclusive. High fat diet significantly decreased total glutathione content in the blood while BEX supplement increased glutathione oxidation. In summary, this study showed that decreased total glutathione concentration in the blood co-occurred with high fat treatment, high anxiety level and low depression level in the mice; and when supplemented in a high fat diet, BEX had anxiolytic effect in the mice.

Keywords

high fat diet; anxiety; depression; glutathione; natural product

Introduction

Increased dietary fat intake is a major causative factor of obesity and overweight (1), which are associated with psychiatric disorders, such as anxiety and depression observed in both human and rodent subjects (2–5). Chronic high fat diet has been shown to impair the

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function of brain by increasing oxidative stress (6, 7), inflammation (8), and inducing insulin resistance (9). However, a keyword-guided Pubmed literature search indicates that currently among hundreds of thousands publications on “high fat diet”, “obesity”, or “overweight”, only 4–5% are relevant to “brain”, implicating that the influences of theses factors on the brain remain an under-investigated field. Therefore it is not surprising that few therapeutic strategies targeting at this link have been developed.

Materials derived from bamboo plants have been used in Traditional Chinese Medicine to treat various diseases (10). *Phyllostachys edulis*, also known as Moso or Maozhu, is one of the fastest growing plants in the world. It is a “running bamboo” with large biomass and wide geographical distribution. Our previous studies have shown that an ethanolic extract derived from this bamboo ameliorates obesity-associated lipotoxicity and inflammation (11–13). In the present study, we further investigated the influences of this bamboo extract (BEX) on anxiety- and depression-like neurobehaviors in mice treated with high fat diet.

Experimental methods

Bamboo extract (BEX)

The BEX used in this study was provided by Golden Basin LLC (Kailua, HI). It is made from fresh leaves and small branches of bamboo *Phyllostachys edulis*, produced in Hunan Province, China, through a patented ethanol/water extraction procedure (Chinese invention patent, CN 1287848A). The raw material was adequately washed in water and dried in air, ground and filtered through screen (< 20 mesh), and then went through infusion extraction in 70%–90% ethanol twice. The extract was filtered to remove particles, and concentrated by vacuuming. There was no excipient material added to the bamboo extract. The manufacturer’s measurement showed that the major composition of the raw BEX includes 50% water, 20% saccharides, 10% protein, and 20% others. Our previous studies demonstrated that the anti-lipotoxicity function of BEX is in the ethanol soluble fraction (12,13). Phenolics constitute ~30% (w/w) of the ethanol exactables, corresponding to ~6% (w/w) of the total dry mass of BEX. Approximately 1/3 of the phenolics are flavonoids (14).

Animals

Male mice with CD-1 genetic background were purchased from Jackson laboratories (Bar Harbor, MN) at 4 weeks, and housed 5 per cage in the laboratory Animal Service facility of University of Hawaii. Animals had access to water and food *ad libitum*. The room temperature was controlled at 20°C and lighting at 12 h intervals. All animal procedures have been approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Hawaii.

Dietary treatment

After one week of acclimation with regular rodent chow, the mice were separated into four groups, with 5 in each group: (1) SC group, fed a standard diet with 10% energy from fat; (2) SB group, fed the standard diet supplemented with BEX (11 g dry mass per 17 MJ); (3) HC group, fed a high fat diet with 45% energy from fat; and (4) HB group, fed the high fat diet supplemented with BEX. All diets were purchased from Research Diets (New

Brunswick, NJ, USA). The dietary composition is listed in Table 1. Calories derived from BEX contributed to approximately 0.66% of the total energy in the diet, and this minor portion is not reflected in the Table. Body weight and food consumption were measured weekly.

Glucose tolerance test

D-(+)-glucose (Sigma, St. Louis, MA) was dissolved in sterile water and delivered to each mouse via intraperitoneal injection at a dosage of 0.75 g/kg body weight after overnight fasting. One drop of blood was collected by tail cut and the blood glucose concentration was monitored at 0, 0.5, 1, 1.5, and 2 h after the glucose injection. Area Under Curve (AUC) was calculated to reflect the glucose tolerance status during the test. This test was carried out 10 days prior to the behavioral tests.

Open Field Test

Using Open Field test to assess anxiety responses of rodents is based on a disinhibition of natural exploratory tendencies by anxiolytic treatments (15). An increase in locomotion or time spent in the central area of the open field without modifications of total locomotion and vertical exploration can be interpreted as an anxiolytic-like effect, while decrease of these parameters is associated with anxiogenic effects. This test has been pharmacologically validated with classical benzodiazepines such as chlordiazepoxide and diazepam that are effective in the treatment of generalized anxiety disorder (16).

The dimension of the Open Field used in this study was 46 cm x 46 cm x 36 cm, with opaque walls. Half-hour prior to the test, mice were transported into the test room, housed singly, and protected from external perturbation. The lighting condition was adjusted to dim in the test room. Each animal was removed from home cage and placed at the center of the open field, a video camera was used to monitor the movement of the animal for 5 min, and the data was analyzed using the TSE videomot2 system (TSE Systems, Inc. Chesterfield, MO). The apparatus was cleaned with Clidox and water, and dried with paper towel between tests.

Hole-Board Test

Similar to Open Field test, Hole-Board test is also based on a disinhibition of natural exploratory tendencies by anxiolytic treatments (15). In this test, the number and duration of head dips have been found to increase dose-dependently upon treatments of diazepam and chlordiazepoxide, and decrease upon exposure to anxiogenic drugs (17). Non-anxiolytic categories of psychoactive drugs do not produce false positive results in this test (15). An Open Field of the same size above but with clear Plexiglas walls was used. The floor was made of opaque plexiglas with 16 holes evenly distributed, each hole is 3.8 cm in diameter and 10 cm deep. The mice were prepared and released as described above. Each mouse was observed and videotaped for 5 min, and the frequency and duration of head-dip were counted. The definition of “head-dip” is: “the animal places its head into one of the holes to a minimum depth such that the ears are level with the floor of the apparatus”. The scoring procedure was not blinded, however, during the test the operator was guided by an identification number on the cage of each mouse and tried not to associate the number with

the dietary treatment of each subject. The apparatus was cleaned with Clidox and water, and dried with paper towel between tests.

Force Swimming

Force swimming test is commonly used for screening antidepressants (18). In this test, rodents are forced to swim in a narrow space from which there is no escape. The animals typically exhibit an initial period of vigorous activity, followed by adopting a characteristic immobile posture, which is interpreted as "behavioral despair". In the present study, a glass baker (24 cm wide, 40 cm deep) was used as the test container. The baker was filled with room temperature (22 °C) water to half volume. The lighting condition in the testing room was adjusted to normal. Each mouse was prepared as described above and released into the water. The movement of the animal was observed and videotaped for 5 min and the immobility time was counted manually using a stopwatch. The water was changed after the test of each mouse. This test was repeated in two consecutive days. Same as in the Hole-Board test, the scoring procedure in the Force Swimming test was not blinded but the operator tried not to pay attention to the type of dietary treatment of each subject. When the test was re-scored through the videotape, similar result was obtained.

Measurements of total and oxidized glutathione

Glutathione (GSH) is the most abundant thiol antioxidant and a sensitive maker of the redox status in mammalian cells. It exists in either reduced (GSH) or oxidized (GSSG) form. To evaluate the influences of the dietary factors on the systemic redox status of the mice, blood was collected from the animals through tail cut after 2 months of dietary treatment, total and oxidized GSH were measured in lysed whole blood using GSH/GSSG-412 assay kit (Oxis, Foster City, CA). The ratio of oxidized GSH/ total GSH was calculated as 2x[GSSG]/[total GSH].

Statistical Methods

Prism 4.0a (GraphPad Software Inc., La Jolla, CA) was used for statistical analyses. Differences among the means were analyzed using one-way ANOVA followed by post-hoc Tukey’s multiple comparison test, or two-way ANOVA followed by Bonferroni post-hoc test. Two-way ANOVA was also used to analyze the influences of BEX, fat content, and their interaction. $P < 0.05$ was considered statistically significant.

Results

Energy intake and body weight

As shown in Table 2, BEX supplement in high fat diet (HB) increased daily energy intake by 22% in comparison to the high fat control (HC), However, no difference in body weight was observed in these two groups. BEX supplement in standard diet did not affect energy intake or body weight in the mice. High fat diet is a significant influential factor on both energy intake and body weight in these mice. Our previous studies have shown that the influence of BEX supplement on energy intake is species- and strain-dependent. For example, BEX supplement in both standard and high fat diet did not affect energy intake or body weight in C57BL/6J mice (11). However, one of our unpublished studies showed that

when fed to Fischer 344 rats, BEX increased energy intake from standard diet by 16% and from high fat diet by 19%, and increased body weight of these rats by 18% and 13%, respectively. The mechanism behind these phenomena is to be further studied.

Glucose tolerance

As shown in Table 2, although high fat diet caused significant increase in body weight of the mice, no differences were observed in fasting glucose levels and glucose tolerance (calculated as AUC) among the four groups of mice. The result indicates that at this time point the changes in body composition in the mice has not started to affect glucose metabolism, which is an important sign of the onset of metabolic syndrome.

Open Field test

In this test, dietary treatment did not affect the horizontal and vertical locomotion of the mice, as shown by total travel distance and number of rearing, respectively (Table 2). One-way ANOVA indicated that the numbers of visit to the central area among the four groups were similar. However, HC group spent 33% less time in the center area compared to SC group, but this decrease was abolished when BEX was supplemented to the high fat diet (HB). Furthermore, BEX in high fat diet also increased center locomotion, i.e. the center travel distance of HB group was not only 68% higher than HC group, but also 30% higher than SC group. Two-way ANOVA showed that BEX supplement significantly influenced the time spent and distance traveled in the central area.

Hole-board test

As an anxiolytic marker, the number of head-dip in the hole-board test decreased by 33% in HC group compared to SC group, and BEX supplement in high fat diet (HB) brought this reading back to the same level as SC. The duration of the head dip showed more complicated changes. i.e. high fat diet dramatically decreased this reading (−86%, HC verse SC), BEX supplement in high fat diet improved this outcome by 157% (HB verse HC), but the same supplement in the standard diet caused a 68% decrease (SB verse SC). The interaction between BEX and dietary fat content was highly significant, and the reason of this interaction is yet to be understood.

Force swimming

Previous publications have documented that mice treated with high fat diet had a higher level of depression (5). To our surprise, force swimming test in the present study showed that high fat diet significantly decreased the immobility time of the mice, implicating a drop of depression level. On Day 1 of the test, the combination of high fat and BEX (HB) resulted in the shortest immobility time, which equals to ~1/5 of that of SC, and ~1/3 of HC, implicating a potential further antidepressant effect of BEX in the context of high fat diet. When this test was repeated on Day 2, dietary fat content remained a highly significant antidepressant factor, but the immobility time of HB group was no longer different from the other groups, which may implicate a memory gain of the HB group from the experience in Day 1.

Glutathione concentration in whole blood

It was previously reported that buthionine-S,R-sulfoximine (BSO)-induced systemic GSH depletion resulted in elevated anxiety level in mice (19). In this study, we used glutathione content in the blood as a biomarker to reflect the systemic redox status in the mice. Table 2 shows that high fat treatment resulted in an over 60% decrease in the total glutathione level in the blood, while BEX supplement increased glutathione oxidation in general (+35%), regardless of the dietary fat content. As a result, the rate of glutathione oxidation (GSSG/total GSH) was the highest in the mice fed BEX-supplemented high fat diet.

Discussion

This study showed that a 2-month exposure of mice with CD-1 genetic background to a high level of saturated dietary fat moderately increased body weight (+14%), but dramatically decreased glutathione concentration in the blood (−62%), which co-occurred with an increase of anxiety in these animals. This observation is consistent with a previous publication that a chemically induced systemic glutathione depletion had anxiogenic effect in mice (19). Correlation between anxiety and oxidative stress has recently been reviewed by Bouayed et al. (20). Contradictory to this widely reported correlation, our study revealed that BEX supplement ameliorated high fat-induced anxiety yet resulted in the highest level of glutathione oxidation in the blood, implicating that the anxiolytic effect of BEX may be mediated through other pathway(s) than its antioxidant (14) function. In a recent review, the NFκB pathway has been highlighted in the activation of inflammation in the central nervous systems (CNS) under the condition of overnutrition (21). Our previous publications have documented that BEX inhibits NFκB and AP-1 activation and thus reduces peripheral production of pro-inflammatory cytokines in mice treated with high fat diet and in cell culture models mimicking such a condition (11, 12). Our unpublished data have associated the anti-inflammatory effect of BEX to its flavonoid content. Therefore it is possible that flavonoids in BEX can directly regulate the inflammatory status of the CNS, and/or influence CNS through ameliorating peripheral inflammation. Furthermore, flavonoids have also been reported as a new family of benzodiazepine receptor ligands (22), however, this has not been studied in the context of high fat diet treatment.

So far very few animal studies on mood and diet have been published. Buchenauer et al. showed that treating Fischer 344 rats with a high fat diet (35%, verse 4% in control diet) for 8 weeks significantly increased the anxiety level (hole-board test) of the rats (4). In contrast, two short-term studies reported anxiolytic effects of high fat diet. Wistar rats fed a high fat diet (63%, verse 21% in control) for 5 days (23), and Sprague-Dawley rats fed a high fat diet (90%, verse 5% in control) for 7 days, both resulted in reduced anxiety levels in elevated plus maze test (24). It is therefore possible that prolonged treatment may convert high fat diet from an anxiolytic to an anxiogenic factor. The treatment in our study is comparable to that used by Buchenauer et al. (4), i.e. approximately 30% increase in calories derived from fat for 8 weeks. Similarly, we also observed that high fat treatment for such a period of time increased anxiety levels of the animals.

The association between oxidative stress and depression has been recently reviewed by Hovatta et al. (25), and increased oxidative stress markers and decreased glutathione level in

serum have been reported in human subjects with major depression. In contrast to these observations, the present study highlighted the co-occurrence of oxidative stress and decreased depression level in mice fed a high fat diet. Furthermore, the highest glutathione oxidation rate in the HB group also coincided with the lowest depression level in these mice in the test on Day 1. In light of previous publications, it seems that the length of high fat diet treatment may be a critical factor in the development of depression. For example, Yamada et al. reported that treating C57BL/6J mice with a high fat diet (60%, verse 12.6% in control) for 16 weeks increased the immobility time in the force swimming test (5). However, Maniam and Morris demonstrated an anti-depressive effect of 8-week post-weaning high fat diet treatment (32%, verse 12% in control) in Sprague–Dawley rats experienced early life stress induced by prolonged maternal separation (26). In our study, the dietary fat content was higher than that used by Maniam and Morris, but the length of treatment was similar. This also indicates that short-term and long-term oxidative stress may have differential influences on mood.

Natural products have been extensively explored for their anxiolytic and anti-depressive effects, and the most recent examples include the use of neem leaf extract (27), lavender oil (28), Bacopa monniera and American Ginseng (29). However, to the best of our knowledge, the present study is the first investigation on the psychiatric effect of a natural product in the context of high fat diet. In summary this study demonstrated a significant systemic redox shift caused by high fat diet treatment in mice, and the opposite changes of anxiety and depression levels in these animals. BEX supplement in high fat diet showed significant anxiolytic effects, and the mechanism of this function needs further investigation.

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Table 1

The composition of the diets used in this study.

Diet	**Standard control (SC)**		**Standard BEX (SB)**		**High fat control (HC)**		**High fat BEX (HB)**	
Ingredient	**g**	**kJ**	**g**	**kJ**	**g**	**kJ**	**g**	**kJ**
Casein, 80 Mesh	200	3349	200	3349	200	3349	200	3349
L-Cystine	3	50	3	50	3	50	3	50
Corn Starch	315	5275	315	5275	72.8	1219	72.8	1219
Maltodextrin 10	35	586	35	586	100	1674	100	1674
Sucrose	350	5862	350	5862	172.8	2894	172.8	2894
Cellulose, BW200	50	0	50	0	50	0	50	0
Soybean Oil	25	942	25	942	25	942	25	942
Lard	20	754	20	754	177.5	6692	177.5	6692
Mineral Mix S10026	10	0	10	0	10	0	10	0
DiCalcium Phosphate	13	0	13	0	13	0	13	0
Calcium Carbonate	5.5	38	5.5	38	5.5	38	5.5	38
Potassium Citrate, 1H2O	16.5	0	16.5	0	16.5	0	16.5	0
Vitamin Mix V10001	10	167	10	167	10	167	10	167
Choline Bitartrate	2	0	2	0	2	0	2	0
Bamboo Extract (dry mass)	0	0	11	0	0	0	11	0
Water from Bamboo Extract	0	0	11	0	0	0	11	0
FD&C Yellow Dye #5	0.05	0	0.025	0	0	0	0.025	0
FD&C Red Dye #40	0	0	0	0	0	0	0.025	0
FD&C Blue Dye #1	0	0	0.025	0	0.05	0	0	0
Total	1055	17000	1077	17000	858	17000	880	17000

Table 2

Influences of dietary treatment on body weight, energy intake, glucose tolerance, systemic redox status, and neurobehaviors of the mice. Average and (SD) are shown. N=5, Mean values within a row without a common letter in the superscripts were significantly different (P<0.05). n.s., non-significant.

	Dietary Treatment (One-way or two-way ANOVA with post-hoc comparison)				Influential Factors (P value of Two-way ANOVA)		
	Standard Control (SC)	**Standard BEX (SB)**	**High fat Control (HC)**	**High fat BEX (HB)**	**BEX**	**Dietary Fat**	**Interaction**
Energy intake (kJ/mouse/day)	42.5 (5.4) [a]	43.0 (6.0) [a]	46.2 (8.1) [a]	56.2 (8.0) [b]	0.042	0.0019	n.s.
Body weight (g)	28.9 (2.2) [a]	29.4 (2.1) [a]	33.2 (3.4) [b]	33.3 (1.8) [b]	n.s.	0.0017	n.s.
Fasting glucose (mg/dl)	107.2 (19.0) [a]	80.1 (18.5) [a]	101.4 (17.3) [a]	100.8 (11.1) [a]	n.s.	n.s.	n.s.
Glucose tolerance (AUC)	417.2 (51.1) [a]	358.0 (65.7) [a]	412.5 (100.9) [a]	379.6 (10.9) [a]	n.s.	n.s.	n.s.
Open Field							
Total distance traveled (cm)	1961.4 (264.8) [a]	2346.0 (515.7) [a]	2279.3 (383.9) [a]	2245.4 (261.0) [a]	n.s.	n.s.	n.s.
Number of Rearing	59 (11.6) [a]	71 (9.4) [a]	62.4 (3.8) [a]	59.2 (12.3) [a]	n.s.	n.s.	n.s.
Number of visits to center	23.2 (9.9) [a]	22.6 (6.0) [a]	18.2 (3.5) [a]	24.8 (3.1) [a]	n.s.	n.s.	n.s.
Time spend in the center (sec)	32.9 (5.1) [a]	34.0 (10.2) [a]	22.1 (4.9) [b]	38.7 (7.9) [a]	0.017	n.s.	0.032
Distance traveled in center (cm)	347.8 (41.1) [a,b]	387.7 (119.1) [a,b,c]	268.6 (92.5) [a]	451.8 (81.6) [c]	0.012	n.s.	n.s.
Hole-Board Test							
Number of head-dip	38 (6.67) [a]	33 (9.38) [a,b]	25.6 (5.27) [b]	43 (9.13) [a]	n.s.	n.s.	0.0055
Duration of head-dip (sec)	94.2 (42.5) [a]	30.0 (9.7) [b]	13.6 (1.3) [c]	34.9 (8.2) [b]	0.047	0.0015	0.0005
Force swimming							
Immobility time, Day 1 (sec)	40.3 (26.1) [a]	47.3 (4.1) [a]	24.0 (5.1) [a,b]	8.8 (7.4) [b]	n.s.	0.0051	n.s.
Immobility time, Day 2 (sec)	36.6 (5.3) [a]	37.7 (15.6) [a]	16.3 (16.1) [a]	15.8 (10.9) [a]	n.s.	0.0079	n.s.
Total GSH in blood (μM)	865.2 (444.6) [a,b]	963.4 (405.0) [a]	358.0 (12.8) [b]	338.0 (326.6) [b]	n.s.	0.0053	n.s.
GSSG in blood (μM)	8.1 (1.3) [a]	34.3 (14.5) [a]	13.3 (13.0) [a]	29.1 (24.2) [a]	0.016	n.s.	n.s.
GSSG/total GSH	0.021 (0.0068) [a]	0.085 (0.045) [a]	0.080 (0.063) [a]	0.26 (0.20) [b]	0.023	0.028	n.s.