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Short Communication

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

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Abstract

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

Key words: High-fat diet: Anxiety: Depression: Glutathione: Natural products

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 subjects and rodents[2–5]. A chronic high-fat diet has been shown to impair the 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 of publications on 'high fat diet', 'obesity' or 'overweight', only 4–5% are relevant to 'brain', implicating that the influences of these 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 a large biomass and a 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 neurobehaviours in mice treated with a high-fat diet.

Experimental methods

Bamboo extract

BEX used in the present study was provided by Golden Basin LLC. It is made from fresh leaves and small branches of

Abbreviations: BEX, bamboo extract; GSH, reduced glutathione; GSSG, oxidised glutathione; HB, high-fat bamboo extract; HC, high-fat control; SB, standard bamboo extract; SC, standard control.

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bamboo (*P. 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 BEX. 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 about 30 % (w/w) of the ethanol exactables, corresponding to about 6 % (w/w) of the total dry mass of BEX. Approximately one-third of the phenolics are flavonoids[14].

Animals

Male mice with CD-1 genetic background were purchased from Jackson Laboratories at 4 weeks, and housed five 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 at the University of Hawaii.

Dietary treatment

After 1 week of acclimatisation with regular rodent chow, mice were separated into four groups, with five in each group: (1) standard control (SC) group, fed a standard diet with 10 % energy from fat; (2) standard BEX (SB) group, fed the standard diet supplemented with BEX (11 g dry mass per 17 MJ); (3) high-fat control (HC) group, fed a high-fat diet with 45 % energy from fat; (4) high-fat BEX (HB) group, fed the high-fat diet supplemented with BEX. All diets were purchased from Research Diets. The dietary composition is listed in Table 1. Energy derived from BEX contributed to approximately 0·66 % of the total energy in the diet, and this minor portion is not reflected in Table 1. Body weight and food consumption were measured weekly.

Glucose tolerance test

D-(+)-Glucose (Sigma) 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. Then, one drop of blood was collected by tail cut and blood glucose concentration was monitored at 0, 0·5, 1, 1·5 and 2 h after the glucose injection. The area under the curve was calculated to reflect the glucose tolerance status during the test. This test was carried out 10 d before the behavioural tests.

Open-field test

Using the 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 a decrease in 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 generalised anxiety disorder[16].

Table 1. The composition of the diets used in the study

Diet…	SC		SB		HC		HB	
	g	kJ	g	kJ	g	kJ	g	kJ
Ingredients								
Casein, 80 mesh	200	3349	200	3349	200	3349	200	3349
L-Cystine	3	50	3	50	3	50	3	50
Maize 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
Soyabean 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, $1H_2O$	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	17 000	1077	17 000	858	17 000	880	17 000

SC, standard control; SB, standard bamboo extract; HC, high-fat control; HB, high fat bamboo extract.

The dimension of the open field used in the present study was 46 cm × 46 cm × 36 cm, with opaque walls. At 0·5 h before 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 the home cage and placed at the centre of the open field, a video camera was used to monitor the movement of the animals for 5 min, and data were analysed using the TSE videomot2 system (TSE Systems, Inc.). The apparatus was cleaned with Clidox and water, and dried with a paper towel between the tests.

Hole-board test

Similar to the open-field test, the 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 as above but with clear Plexiglas walls was used. The floor was made of opaque Plexiglas with sixteen holes evenly distributed; each hole is 3·8 cm in diameter and 10 cm deep. Mice were prepared and released as described above. Each mouse was observed and videotaped for 5 min, and the frequency and duration of head dips were counted. The definition of 'head dip' is as follows: '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 a paper towel between the tests.

Force swimming

The 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 'behavioural 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 animals 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. As with 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, a similar result was obtained.

Measurements of total and oxidised 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 oxidised (GSSG) form. To evaluate the influences of the dietary factors on the systemic redox status of mice, blood was collected from the animals through tail cut after 2 months of dietary treatment. Total and GSSG were measured in lysed whole blood using the GSH/GSSG-412 assay kit (Oxis). The ratio of GSSG:total GSH was calculated as 2 × (GSSG)/(total GSH).

Statistical methods

Prism 4.0a (GraphPad Software, Inc.) was used for statistical analyses. Differences among the means were analysed using one-way ANOVA followed by *post hoc* Tukey's multiple comparison test, or two-way ANOVA followed by the Bonferroni *post hoc* test. Two-way ANOVA was also used to analyse 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, the BEX supplement in the high-fat diet (HB) increased daily energy intake by 22% in comparison with the HC. However, no difference in body weight was observed in these two groups. The BEX supplement in the standard diet did not affect energy intake or body weight in mice. The 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, the BEX supplement in both the 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 the standard diet by 16% and from the high-fat diet by 19%, and increased the 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 the high-fat diet caused a significant increase in the body weight of mice, no differences were observed in fasting glucose levels and glucose tolerance (calculated as the area under the curve) among the four groups of mice. The result indicates that at this time point, the changes in body composition in mice have not started to affect glucose metabolism, which is an important sign of the onset of the metabolic syndrome.

Table 2. Influences of dietary treatment on body weight, energy intake, glucose tolerance, systemic redox status and neurobehaviours of mice

(Mean values and standard deviations, *n* 5)

	Dietary treatment (one-way or two-way ANOVA with *post hoc* comparison)								Influential factors (*P* value of two-way ANOVA)		
	SC		SB		HC		HB				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	BEX	Dietary fat	Interaction
Energy intake (kJ/mouse per d)	42·5[a]	5·4	43·0[a]	6·0	46·2[a]	8·1	56·2[b]	8·0	0·042	0·0019	NS
Body weight (g)	28·9[a]	2·2	29·4[a]	2·1	33·2[b]	3·4	33·3[b]	1·8	NS	0·0017	NS
Fasting glucose (mg/l)	1072[a]	190	801[a]	185	1014[a]	173	1008[a]	111	NS	NS	NS
Glucose tolerance (AUC)	417·2[a]	51·1	358·0[a]	65·7	412·5[a]	100·9	379·6[a]	10·9	NS	NS	NS
Open-field test											
Total distance travelled (cm)	1961·4[a]	264·8	2346·0[a]	515·7	2279·3[a]	383·9	2245·4[a]	261·0	NS	NS	NS
Number of rearing	59[a]	11·6	71[a]	9·4	62·4[a]	3·8	59·2[a]	12·3	NS	NS	NS
Number of visits to the centre	23·2[a]	9·9	22·6[a]	6·0	18·2[a]	3·5	24·8[a]	3·1	NS	NS	NS
Time spent in the centre (s)	32·9[a]	5·1	34·0[a]	10·2	22·1[b]	4·9	38·7[a]	7·9	0·017	NS	0·032
Distance travelled in the centre (cm)	347·8[a,b]	41·1	387·7[a,b,c]	119·1	268·6[a]	92·5	451·8[c]	81·6	0·012	NS	NS
Hole-board test											
Number of head dips	38[a]	6·67	33[a,b]	9·38	25·6[b]	5·27	43[a]	9·13	NS	NS	0·0055
Duration of head dips (s)	94·2[a]	42·5	30·0[b]	9·7	13·6[c]	1·3	34·9[b]	8·2	0·047	0·0015	0·0005
Force swimming											
Immobility time, day 1 (s)	40·3[a]	26·1	47·3[a]	4·1	24·0[a,b]	5·1	8·8[b]	7·4	NS	0·0051	NS
Immobility time, day 2 (s)	36·6[a]	5·3	37·7[a]	15·6	16·3[a]	16·1	15·8[a]	10·9	NS	0·0079	NS
Total GSH in blood (μM)	865·2[a,b]	444·6	963·4[a]	405·0	358·0[b]	12·8	338·0[b]	326·6	NS	0·0053	NS
GSSG in blood (μM)	8·1[a]	1·3	34·3[a]	14·5	13·3[a]	13·0	29·1[a]	24·2	0·016	NS	NS
GSSG:total GSH	0·021[a]	0·0068	0·085[a]	0·045	0·080[a]	0·063	0·26[b]	0·20	0·023	0·028	NS

SC, standard control; SB, standard bamboo extract; HC, high-fat control; HB, high fat bamboo extract; BEX, bamboo extract; AUC, area under the curve; GSH, reduced glutathione; GSSG, oxidised glutathione.
[a,b,c] Mean values within a row with unlike superscript letters were significantly different ($P<0·05$).

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Open-field test

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

Hole-board test

As an anxiolytic marker, the number of head dips in the hole-board test decreased by 33 % in the HC group compared with the SC group, and the BEX supplement in the high-fat diet (HB) brought this reading back to the same level as SC. The duration of head dips showed more complicated changes, i.e. the high-fat diet dramatically decreased this reading (−86 %, HC *v.* SC), whereas the BEX supplement in the high-fat diet improved this outcome by 157 % (HB *v.* HC), but the same supplement in the standard diet caused a 68 % decrease (SB *v.* 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 a high-fat diet had a higher level of depression[5]. To our surprise, the force-swimming test in the present study showed that the high-fat diet significantly decreased the immobility time of mice, implicating a drop of depression level. On day 1 of the test, the combination of the high-fat diet and BEX (HB) resulted in the shortest immobility time, which equals to about one-fifth of that of SC, and about one-third of HC, implicating a potential further antidepressant effect of BEX in the context of the 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 the 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 the whole blood

It has previously been reported that buthionine-*S*,*R*-sulfoximine-induced systemic GSH depletion resulted in elevated anxiety level in mice[19]. In the present study, we used glutathione content in the blood as a biomarker to reflect the systemic redox status in mice. Table 2 shows that the high-fat treatment resulted in an over 60 % decrease in the total glutathione level in the blood, while the 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 mice fed the BEX-supplemented high-fat diet.

Discussion

The present 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 in anxiety in these animals. This observation is consistent with a previous publication that a chemically induced systemic glutathione depletion had an anxiogenic effect in mice[19]. The correlation between anxiety and oxidative stress has recently been reviewed by Bouayed *et al.*[20]. Contradictory to this widely reported correlation, the present study revealed that the 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 NF-κB pathway has been highlighted in the activation of inflammation in the central nervous system under the condition of overnutrition[21]. Our previous publications have documented that BEX inhibits NF-κB and activator protein 1 (AP-1) activation and thus reduces peripheral production of pro-inflammatory cytokines in mice treated with a high-fat diet and in cell-culture models mimicking such a condition[11,12]. Recent work has associated the anti-inflammatory effect of BEX with its flavonoid content (JK Higa, unpublished results). Therefore, it is possible that flavonoids in BEX can directly regulate the inflammatory status of the central nervous system, and/or influence the central nervous system 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 a high-fat diet treatment.

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

The association between oxidative stress and depression has recently been 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 a high-fat diet treatment may be a critical factor in the development of depression. For example, Yamada *et al.*[5] reported that treating C57BL/6J mice with a high-fat diet (60 % *v.* 12·6 % in the control) for 16 weeks increased the immobility time in the force-swimming test. However, Maniam & Morris[26] demonstrated an anti-depressive effect of an 8-week post-weaning high-fat diet treatment (32 % *v.* 12 % in the control) in Sprague–Dawley rats that experienced early-life stress induced by prolonged maternal separation. In the present study, the dietary fat content was higher than that used by Maniam & 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 a high-fat diet. In summary, the present study demonstrated a significant systemic redox shift caused by a high-fat diet treatment in mice, and the opposite changes in anxiety and depression levels in these animals. The BEX supplement in the high-fat diet showed significant anxiolytic effects, and the mechanism of this function needs further investigation.

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