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Involvement of catecholaminergic and GABAAergic mediations in the anxiety-related behavior in long-term powdered diet-fed mice

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ABSTRACT

Dietary habits are important factors which affect metabolic homeostasis and the development of emotion. We have previously shown that long-term powdered diet feeding in mice increases spontaneous locomotor activity and social interaction (SI) time. Moreover, that diet causes changes in the dopaminergic system, especially increased dopamine turnover and decreased dopamine D4 receptor signals in the frontal cortex. Although the increased SI time indicates low anxiety, the elevated plus maze (EPM) test shows anxiety-related behavior and impulsive behavior. In this study, we investigated whether the powdered diet feeding causes changes in anxiety-related behavior. Mice fed a powdered diet for 17 weeks from weaning were compared with mice fed a standard diet (control). The percentage (%) of open arm time and total number of arm entries were increased in powdered diet-fed mice in the EPM test. We also examined the effects of diazepam, benzodiazepine anti-anxiety drug, bicuculline, GABA-A receptor antagonist, methylphenidate, dopamine transporter (DAT) and noradrenaline transporter (NAT) inhibitor, atomoxetine, selective NAT inhibitor, GBR12909, selective DAT inhibitor, and PD168077, selective dopamine D4 receptor agonist, on the changes of the EPM in powdered diet-fed mice. Methylphenidate and atomoxetine are clinically used to treat attention deficit/hyperactivity disorder (ADHD) symptoms. The % of open arm time in powdered diet-fed mice was decreased by treatments of atomoxetine, methylphenidate and PD168077. Diazepam increased the % of open arm time in control diet-fed mice, but not in powdered diet-fed mice. The powdered diet feeding induced a decrease in GABA transaminase, GABA metabolic enzymes, in the frontal cortex. Moreover, the powdered diet feeding induced an increase in NAT expression, but not DAT expression, in the frontal cortex. These results suggest that the long-term powdered diet feeding may cause low anxiety or impulsivity, possibly via noradrenergic and/or dopaminergic, and GABAAergic mediations and increase the risk for onset of ADHD-like behaviors.

1. Introduction

Various changes brought on by modern lifestyle have caused an increased risk of disease. Dietary habits are particularly important factors which affect development of the central nervous system as well as emotion (Aoki et al., 2005; Kushida et al., 2008; Mitome et al., 2005; Niijima-Yaoita et al., 2013; Yamamoto and Hirayama, 2001). It has been suggested that evolutionary changes in dietary habit to softer foods in part explain lesser developed masticatory function (Yamanaka et al., 2009). We recently reported that long-term powdered diet feeding in mice increases spontaneous locomotor activity and social interaction (SI) time of SI test. Moreover, this diet causes changes in the dopaminergic system, in particular, increased dopamine turnover and decreased dopamine D4 receptor signals in the frontal cortex (Niijima-Yaoita et al., 2013). However, some reports suggest that the impairment of dopaminergic activity in the hippocampus may be related to the

Abbreviations: ADHD, attention deficit/hyperactivity disorder; ANOVA, analysis of variance; BZD, benzodiazepines; DAT, dopamine transporter; EPM, elevated plus maze; GABA-A, γ−amino butyric acid receptor type A; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; i.p., intraperitoneally; NA, noradrenaline; NAT, noradrenaline transporter; % of open arm time, percentage of time spent in the open arm; SI, social interaction; T-PBS, Tween-20 in phosphate-buffered saline

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masticatory dysfunction induced by powdered diet feeding (Kushida et al., 2008; Yoshino et al., 2012).

In addition to the SI test, the elevated plus maze (EPM) test is useful for evaluating anxiety-related behavior (File, 1992). It is known that γ−amino butyric acid type A (GABA-A) receptor plays a critical role in anxiolytic activity. GABA-A receptor is a chloride channel composed of a pentameric hetero-oligometric protein with binding sites for GABA, benzodiazepines (BZD), barbiturates, and steroids, etc. The activation of the GABA-A receptor induced by BZD including diazepam increases the percentage (%) of open arm time in the EPM test, indicating low anxiety (i.e. anxiolytic effect) (for review see Jacob et al., 2008; Möhler et al., 2002). On the other hand, Hwang et al. (2004) reported that the increase in expression of GABA transaminase and GABA metabolic enzymes, provide important information about the brain with GABA dysfunction. Moreover, the GABA transaminase has been primarily investigated in relation to epilepsy, but it has also been found that a decrease in GABA neurotransmission appears to be involved in the aetiology of several neurological disorders such as anxiety (for review see Kowalczyk and Kulig, 2014).

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by inattention, hyperactivity, and impulsivity. Using the ADHD animal model, impulsive behavior can be evaluated by the EPM test (Kishikawa et al., 2014; Niimi et al., 2011; Ueno et al., 2002). This test is designed to detect anxiety-related behavior but it also reflects impulsivity for novelty seeking.

The frontal cortex is an important brain region which is related to ADHD symptoms, including impulsive behavior (for reviews see Arnsten and Pliszka, 2011; Brevet-Aeby et al., 2016; Herman et al., 2018). The etiology and pathophysiology of ADHD have not been completely clarified, however the prefrontal cortex is known to be particularly sensitive to the neurochemical environment; relatively slight changes in the levels of noradrenaline (NA) and dopamine can produce significant changes in its function (for review see Arnsten and Pliszka, 2011). Although newer drugs have been developed, methylphenidate and atomoxetine remain the predominantly prescribed drugs for the treatment of ADHD. Methylphenidate increases extracellular dopamine and NA indirectly by blocking the transporters, dopamine transporter (DAT) and NA transporter (NAT), while atomoxetine preferentially inhibits NAT (for review see Arnsten and Pliszka, 2011).

The aims of the present mice study on were to investigate the following: (a) whether long-term powdered diet feeding induces changes in anxiety-related behavior in the EPM test, (b) the effect of diazepam, benzodiazepine anti-anxiety drug, bicuculline, a GABA-A receptor antagonist, GBR12909, a selective DAT inhibitor, methylphenidate, DAT and NAT inhibitor, atomoxetine, a selective NAT inhibitor and PD168077, a selective dopamine D4 receptor agonist, on the changes in the EPM test, and (c) GABA transaminase expressions in the frontal cortex, DAT and NAT expressions in the frontal cortex and hippocampus.

2. Materials and methods

2.1. Animal treatment

Male Balb/c mice (3 weeks old) were obtained from Japan CREA (Tokyo, Japan). The animals were housed under conditions of constant temperature (23 ± 1 °C) and humidity (55 ± 5%), on a 12/12 h light–dark cycle (light from 7 to 19 h; dark from 19 to 7 h). The mice were housed in groups of 5–6 in standard plastic cages (30 cm × 20 cm x 14 cm high) with wire mesh lids and a bedding of wood shavings. Mice were fed either a control diet (pellet type Labo MR stock, Nihon Nosan, Kanagawa, Japan) or powdered diet (powder type Labo MR stock, Nihon Nosan) containing the same ingredients with free access to water for 17 weeks. All experiments complied with the Guidelines for Care and Use of Laboratory Animals issued by Tohoku Medical and Pharmaceutical University.

2.2. Drugs and treatment

The following drugs were used: diazepam (Sigma–Aldrich, St. Louis, MO, USA), bicuculline (GABA-A receptor antagonist, Tocris Bioscience, Bristol, UK), methylphenidate (Novartis Pharma, Tokyo, Japan), atomoxetine (selective NET inhibitor, Sigma–Aldrich) and GBR12909 (selective DAT inhibitor, Tocris Bioscience). Diazepam, bicuculline and PD168077 (selective dopamine D4 receptor agonist, Sigma–Aldrich) were suspended in saline containing 0.5% Tween 80. Methylphenidate, atomoxetine and GBR12909 were dissolved in saline. All drugs were administered intraperitoneally (i.p.) (volume: 0.1 ml/10 g body weight) at 30 min before the behavioral test. The drug doses used in the present study were within the ranges widely used in experiments on mice and rats (Gould et al., 2005; Hiraide et al., 2013; Kanegawa et al., 2010; Leggio et al., 2011; Niijima et al., 2006; Niijima-Yaoita et al., 2013; Robinson et al., 2012; Ueno et al., 2002).

2.3. EPM test

At 20 weeks of age, the anxiety-related behavior was evaluated using the EPM test. The apparatus consisted of two open arms (6 cm × 30 cm) opposite each other, crossed by two closed arms (6 cm × 30 cm) (walls 10 cm) with an open roof and central platform (9 cm × 9 cm). The maze floor and walls were constructed from acrylic plate and elevated 40 cm from the ground floor. Initially, the animals were placed on the central platform of the maze in front of a closed arm. The animal had 5 min to explore the apparatus. Activity of mice was monitored via video camera positioned above the apparatus. The time spent in each arm and the number of entries into each arm were automatically analyzed offline using the ANY-maze video tracking software (Stoelting Company, Wood Dale, IL, USA). The test area was cleaned with 20% ethanol between each session.

2.4. Western blot analysis of GABA transaminase in the frontal cortex and both NAT and DAT expressions in the frontal cortex and hippocampus

After 17 weeks of treatment, animals were sacrificed by decaptation without anesthesia. The brains were rapidly resected and two brain regions (frontal cortex and hippocampus) were dissected, and placed on an ice-cold plate. Each brain sample was quickly frozen and stored at −80 °C, until use. The dissected tissues were homogenized in CelLyticTM MT Cell Lysis Reagent (Sigma–Aldrich) containing 1% protease inhibitor cocktail (Sigma-Aldrich) and centrifuged at 15,000 × *g* for 15 min at 4 °C. Supernatants were isolated and protein concentrations were measured using the Pierce BCA protein assay kit (Pierce, Rockford, lL). Equivalent amounts of protein lysates (15 μg) were separated by electrophoresis on a sodium dodecylsulphate polyacrylamide gel (10% e-PAGEL, ATTO Corp., Tokyo, Japan) and transferred onto polyvinylidene fluoride membranes (Immobilon-P, Millipore, Bedford, MA). Blots were blocked for 1 h with Blocking One (Nacalai Tesque, Kyoto, Japan) at room temperature. The membranes were sequentially incubated overnight with antibodies to NAT (Norepinephrine Transporter Monoclonal Antibody, dilution 1: 2000, P21934, Thermo Scientific, Rockford, lL), DAT (Anti-Dopamine Transporter N-terminal Antibody, dilution 1:1000, D6944, Sigma–Aldrich), GABA transaminase (ABAT Antibody, dilution 1:10000, NBP1-95517, Novus Biologicals, CO) or glyceraldehyde-3-phosphate dehydrogenase (GAPDH, dilution 1:1000, 5714, Cell Signaling Technology, Danvers, MA). After repeated washing with 0.05% Tween-20 in phosphate-buffered saline (T-PBS), a peroxide-conjugated goat anti-mouse antibody (dilution 1:5000, NA931, Amersham, GE Healthcare, Buckinghamshire, UK) for the membrane of NAT, a peroxide-conjugated goat anti-rabbit antibody (dilution 1:5000, 7074, Cell Signaling Technology) for DAT, GABA transaminase or GAPDH, was added for 1 h at room temperature. After repeated washing with T-PBS, the immunoreactive bands were visualized using

ECL Western Blotting Detection Reagents (GE Healthcare) and detected by Image Quant LAS4010 (GE Healthcare). Immunoblots were quantified by Image Quant TL software (GE Healthcare).

2.5. Statistical analyses

Statistical analyses were performed with the computer program, GraphPad Prism (GraphPad Software, Inc., San Diego, CA, USA). Results are expressed as means ± standard errors of the mean (SEM). To analyze the drug's effect on powdered diet group, the results were analyzed by a one-way analysis of variance (ANOVA) using GraphPad Prism, followed by Dunnett's test. To evaluate the effects of diazepam on the EPM test in both control diet and powdered diet groups, two-way ANOVA was used. Significant main effects or interactions were followed by Tukey's test. Statistical evaluations between two groups were performed using Student's *t*-test. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Anxiety-related behavior of powdered diet-fed mice assessed by the EPM test

At 20 weeks of age, the anxiety-related behavior of powdered diet-fed group was measured for 5 min in the EPM apparatus. Fig. 1 shows the influence of powdered diet feeding on the % of open arm time and total number of arm entries. The powdered diet group had a significantly increased % of open arm time (unpaired *t*-test: $p = 0.0017$) (Fig. 1A) and the total number of arm entries (unpaired *t*-test: $p = 0.0111$) (Fig. 1B).

3.2. Effect of diazepam on the anxiety-related behavior of powdered diet-fed mice in the EPM test

To study the implication of influence of anxiolytic agent on the anxiety-related behaviors elicited by powdered diet, mice at 20 weeks of age were used; the % of open arm time and the total number of arm entries were measured in powdered diet- and control diet groups. Fig. 2 shows the % of open arm time and the total number of arm entries after treatment with diazepam, an anxiolytic agent, on powdered diet- and control diet-fed mice. Two-way ANOVA revealed the main effect for diet on the % of open arm time [F (1, 42) = 16.21, $p = 0.0002$], the main effect for drug [F (1, 42) = 18.33, $p = 0.0001$] and diet × drug interaction [F (1, 42) = 4.004, $p = 0.0519$] (Fig. 2A). The post hoc Tukey's test revealed that diazepam (1 mg/kg) significantly increased the % of open arm time in control diet-fed group, compared with that of vehicle-treated control diet-fed mice ($p < 0.01$, Fig. 2A). The % of open time in vehicle-treated powdered diet-fed mice significantly increased, compared with vehicle-treated control diet-fed mice ($p < 0.01$, Fig. 2A). In contrast to the % of open arm time, two-way ANOVA revealed the main effect for diet on the total number of arm entries [F (1, 42) = 8.119, $p = 0.0068$], the main effect for drug [F (1, 42) = 7.985, $p = 0.0072$] and diet × drug interaction [F (1, 42) = 0.1310, $p = 0.7192$] (Fig. 2B). The post hoc Tukey's test revealed that the total number of arm entries in the vehicle-treated powdered diet-fed mice significantly increased, compared with vehicle-treated control diet-fed mice ($p < 0.05$, Fig. 2B).

3.3. Effect of bicuculline, a GABA-A receptor antagonist, on the anxiety-related behavior of powdered diet-fed mice in the EPM test

In the experiments described above, treatment with diazepam increased the % of open arm time in control diet-fed group, but not in the powdered diet-fed group, suggesting that the alteration of GABA-A receptor function. Fig. 3 shows the % of open arm time and the total number of arm entries after treatment with bicuculline, a GABA-A receptor antagonist, on powdered diet-fed mice. The increase in the % of open arm time elicited by powdered diet feeding was attenuated by treatment with bicuculline at a dose of 5 mg/kg, compared with that of vehicle-treated powdered diet-fed group (unpaired *t*-test: $p = 0.0181$, Fig. 3A). However, the total number of arm entries in powdered diet-fed group [unpaired *t*-test: $p = 0.312$, Fig. 3B], after treatment with bicuculline (5 mg/kg) did not show any behavioral changes as compared with the vehicle-treated powdered diet-fed group. There were no significant differences between vehicle-treated control diet-fed mice and bicuculline (5 mg/kg)-treated control diet-fed mice, in the EPM test (data not shown).

3.4. Effect of GBR12909, a selective DAT transporter inhibitor, on the anxiety-related behavior of powdered diet-fed mice in the EPM test

We recently reported that mice subjected to long-term feeding on powdered diet induces the alteration of dopaminergic regulation, and in particular, it decreases the expression of dopamine D4 receptor mRNA and increases dopamine turnover in the frontal cortex (Niijima-Yaoita et al., 2013). To study the influence of selective DAT inhibitor on the anxiety-related behaviors elicited by powdered diet, the % of open arm time and the total number of arm entries after treatment with selective DAT transporter inhibitor were measured in powdered diet group. Fig. 4 shows the % of open arm time and the total number of arm entries after treatment with GBR12909, a selective DAT inhibitor, in powdered diet-fed mice. One-way ANOVA of the influence of GBR12909 on the % of open arm time [F (2, 35) = 1.551; $p = 0.2263$] (Fig. 4A) and total number of arm entries [F (2, 35) = 1.395; $p = 0.2612$] (Fig. 4B) in powdered diet-fed group revealed no significant differences. There were no significant differences between vehicle-treated control diet-fed mice and GBR 12909 (3 mg/kg)-treated control diet-fed mice, in the EPM test (data not shown).

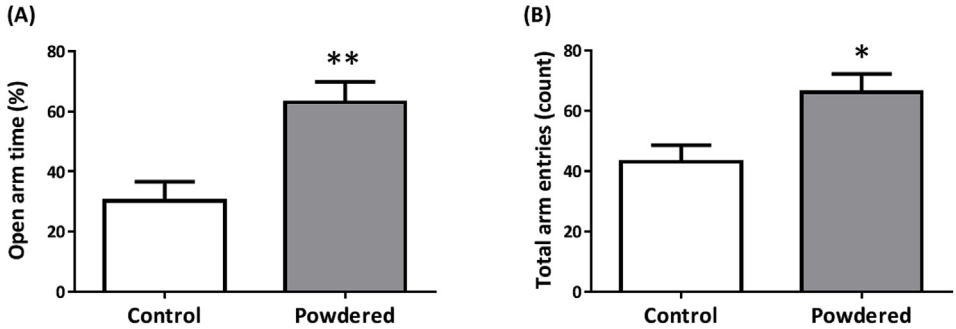

Fig. 1. Influence of powdered diet feeding for 17 weeks on the elevated plus maze test in mice. The left and right panels show time spent in the open arm (A) and total arm entries (B), respectively. The data are expressed as the mean ± S.E.M. for 14–18 mice/group. *$p < 0.05$, **$p < 0.01$; vs. control diet-fed mice (unpaired *t*-test).

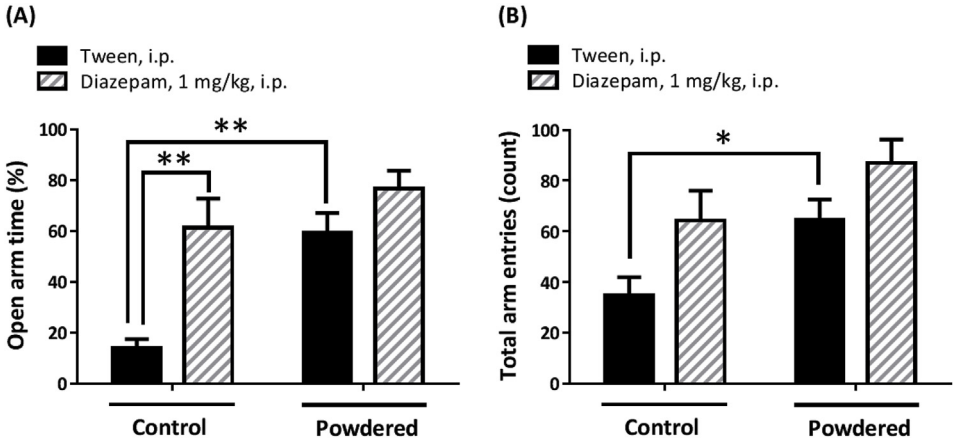

Fig. 2. Effect of diazepam on the elevated plus maze test in control diet- and powdered diet-fed mice. The left and right panels show time spent in the open arm (A) and total arm entries (B), respectively. The data are expressed as the mean ± S.E.M. for 8–15 mice/group. *$p < 0.05$, **$p < 0.01$; vs. vehicle-treated control diet-fed mice (Tukey's test).

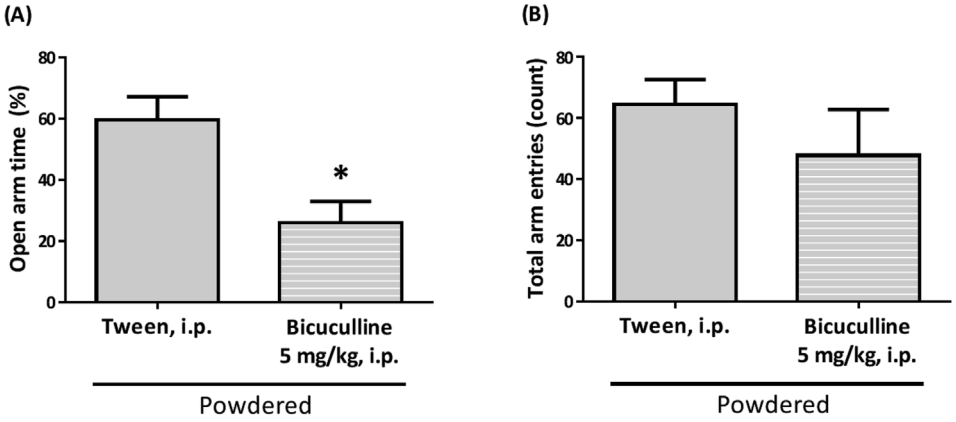

Fig. 3. Effect of bicuculline on the elevated plus maze test in powdered diet-fed mice. The left and right panels show time spent in the open arm (A) and total arm entries (B), respectively. The data are expressed as the mean ± S.E.M. for 6–15 mice/group. *$p < 0.05$; vs. vehicle-treated mice (unpaired *t*-test).

3.5. Effect of atomoxetine, a selective NAT inhibitor, on the anxiety-related behavior of powdered diet-fed mice in the EPM test

To study the influence of selective NAT inhibitor on the anxiety-related behaviors elicited by powdered diet, the % of open arm time and the total number of arm entries after treatment with selective NAT transporter inhibitor were measured in powdered diet group. Fig. 5 shows the % of open arm time and the total number of arm entries after treatment with atomoxetine, a selective NAT inhibitor, in powdered diet-fed mice. One-way ANOVA of the influence of atomoxetine on the % of open arm time in powdered diet-fed group revealed significant differences [F (4, 58) = 3.851; $p = 0.0077$] (Fig. 5A). The post hoc Dunnett's test revealed that atomoxetine at a dose of 0.18 mg/kg, significantly attenuated the % of open arm time in powdered diet-fed group, compared with that of saline-treated powdered diet-fed group ($p < 0.01$, Fig. 5A). One the other hand, one-way ANOVA revealed that the total number of arm entries in powdered diet-fed group [F (4, 58) = 0.2623; $p = 0.9009$, Fig. 5B] was not influenced by treatment with atomoxetine. There were no significant differences between saline-treated control diet-fed mice and atomoxetine (0.18 and 0.5 mg/kg)-treated control diet-fed mice, in the EPM test (data not shown).

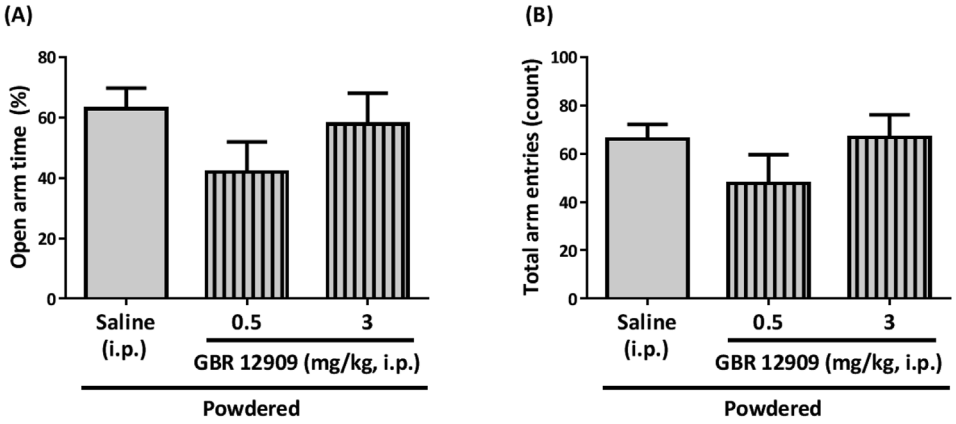

Fig. 4. Effect of GBR12909 on the elevated plus maze test in powdered diet-fed mice. The left and right panels show time spent in the open arm (A) and total arm entries (B), respectively. The data are expressed as the mean ± S.E.M. for 10–18 mice/group.

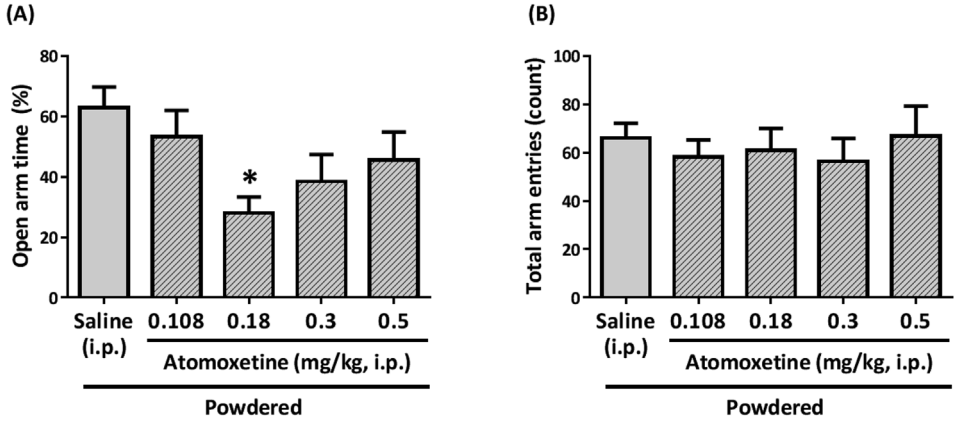

Fig. 5. Effect of atomoxetine on the elevated plus maze test in powdered diet-fed mice. The left and right panels show time spent in the open arm (A) and total arm entries (B), respectively. The data are expressed as the mean ± S.E.M. for 10–18 mice/group. $^{**}p < 0.01$; vs. saline-treated mice (Dunnett's test).

3.6. Effect of methylphenidate, a DAT and NAT inhibitor, on the anxiety-related behavior of powdered diet-fed mice in the EPM test

To study the influence of methylphenidate, a DAT and NAT inhibitor, on the anxiety-related behaviors elicited by powdered diet, the % of open arm time and the total number of arm entries after treatment with methylphenidate (0.133, 0.2 and 0.3 mg/kg) were measured in powdered diet group. Fig. 6 shows the % of open arm time and the total number of arm entries after treatment with methylphenidate in powdered diet-fed mice. One-way ANOVA of the influence of methylphenidate on the % of open arm time in powdered diet-fed group revealed significant differences [F (3, 46) = 2.839; $p = 0.0482$] (Fig. 6A). The post hoc Dunnett's test revealed that methylphenidate (0.2 mg/kg), significantly attenuated the % of open arm time in powdered diet-fed group, compared with that of saline-treated powdered diet-fed group (saline vs. 0.2 mg/kg; $p < 0.05$, Fig. 6A). In contrast, one-way ANOVA revealed that the total number of arm entries in the powdered diet-fed group [F (3, 46) = 1.408; $p = 0.2525$, Fig. 6B] was not influenced by treatment with methylphenidate. There were no significant differences between saline-treated control diet-fed mice and methylphenidate (0.2 and 0.3 mg/kg)-treated control diet-fed mice, in the EPM test (data not shown).

3.7. Effect of PD168077, a selective dopamine D4 receptor agonist, on the anxiety-related behavior of powdered diet-fed mice in the EPM test

We recently reported that PD168077, a selective D4 receptor agonist, attenuates the increased SI time in powdered diet-fed mice (Niijima-Yaoita et al., 2013). To study the influence of PD168077 on the anxiety-related behaviors elicited by powdered diet, the % of open arm time and the total number of arm entries after treatment with PD168077 (0.1 and 0.3 mg/kg) were measured in powdered diet group. Fig. 7 shows the % of open arm time and the total number of arm entries after treatment with PD168077 on powdered diet-fed mice. One-way ANOVA of the influence of PD168077 on the % of open arm time revealed significant differences in powdered diet-fed mice [F (2, 23) = 5.651; $p = 0.0101$, Fig. 7A]. The post hoc Dunnett's test revealed that PD168077 (0.3 mg/kg) significantly attenuated the % of open arm time in powdered diet-fed group, compared with that of vehicle-treated powdered diet-fed mice (vehicle vs. 0.3 mg/kg; $p < 0.05$, Fig. 7A). In contrast to the % of open arm time in powdered diet-fed group, the total number of arm entries in powdered diet-fed group [F (2, 23) = 0.8001; $p = 0.4614$, Fig. 7B] was not influenced by treatment with PD168077. There were no significant differences between vehicle-treated control diet-fed mice and PD168077 (0.3 mg/kg)-treated control diet-fed mice, in the EPM test (data not shown).

3.8. Influence of long-term powdered diet feeding on the expression of GABA transaminase in the frontal cortex

In the experiments described above, the increase in the % of open arm time elicited by long-term powdered diet feeding was attenuated by treatment with bicuculline, GABA-A receptor antagonist. Hwang et al. (2004) suggested that the increase in expression of GABA transaminase, GABA metabolic enzymes (for review see Kowalczyk and Kulig, 2014), provides important information about the brain with

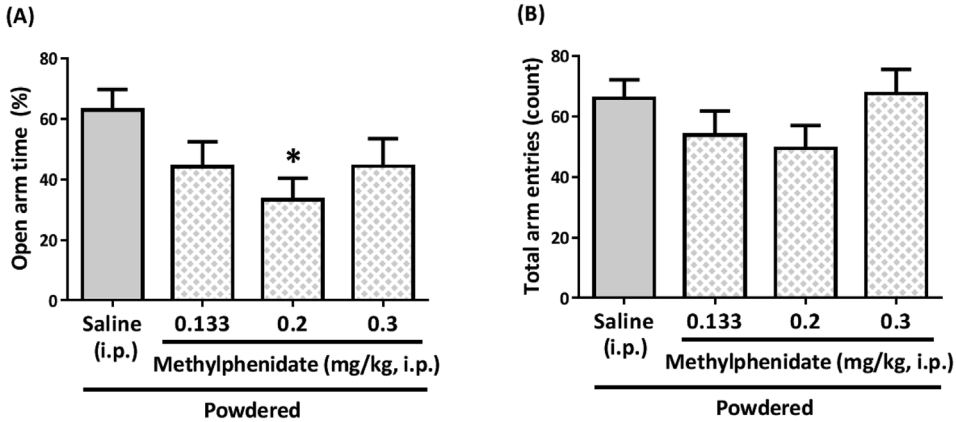

Fig. 6. Effect of methylphenidate on the elevated plus maze test in powdered diet-fed mice. The left and right panels show time spent in the open arm (A) and total arm entries (B), respectively. The data are expressed as the mean ± S.E.M. for 10–18 mice/group. $^{*}p < 0.05$; vs. saline-treated mice (Dunnett's test).

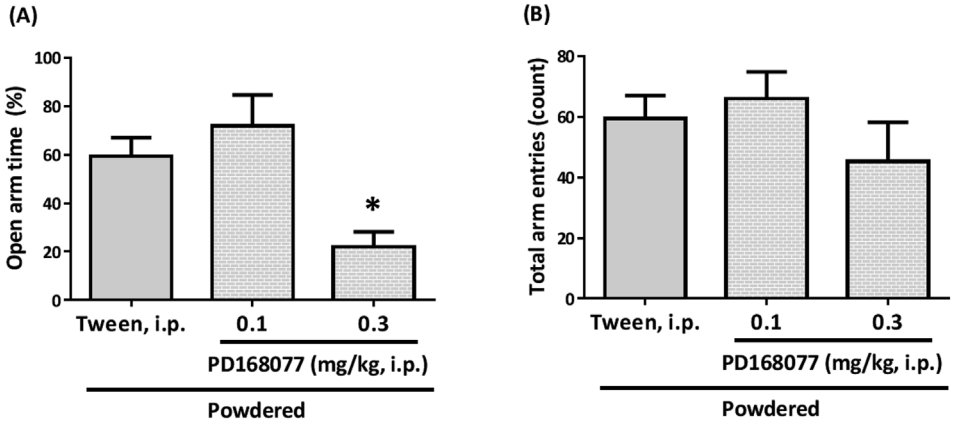

Fig. 7. Effect of PD168077 on the elevated plus maze test in powdered diet-fed mice. The left and right panels show time spent in the open arm (A) and total arm entries (B), respectively. The data are expressed as the mean ± S.E.M. for 5–15 mice/group. *$p < 0.05$; vs. vehicle-treated mice (Dunnett's test).

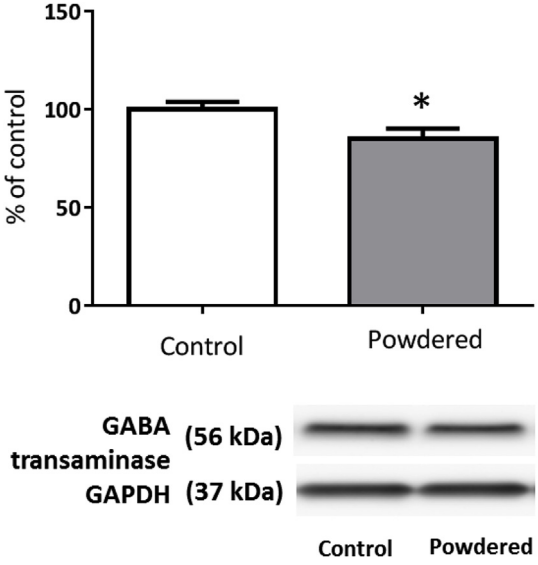

Fig. 8. Influence of powdered diet feeding for 17 weeks on the expression of GABA transaminase in the frontal cortex (FC) of mice. The data are given as the mean ± SEM for a group of 5 mice/group. *$p < 0.05$; vs. control diet-fed mice (unpaired *t*-test).

GABA dysfunction. Therefore, we compared the differences in the expression levels of GABA transaminase in the frontal cortex between the powdered diet group and control diet group (Fig. 8). The levels of GABA transaminase expression in the frontal cortex of powdered diet-fed mice were lower than that of control diet-fed mice (unpaired *t*-test: $p = 0.026$, Fig. 8).

3.9. Influence of long-term powdered diet feeding on the expression of DAT and NAT in the frontal cortex and hippocampus

In the experiments described above, increase in the % of open arm time elicited by long-term powdered diet feeding was attenuated by treatment with atomoxetine, selective NAT inhibitor, and methylphenidate, DAT and NAT inhibitor, but not treatment with GBR12909, a selective DAT inhibitor (Figs. 4–6). Moreover, we recently reported the alteration of dopaminergic regulation, especially the increase in dopamine turnover in the frontal cortex, but not but in the hippocampus of powdered diet-fed mice (Niijima-Yaoita et al., 2013). Therefore, we compared the differences in the expression levels of both DAT and NAT in the frontal cortex and hippocampus between the powdered diet group and control diet group (Figs. 9 and 10). The levels of NAT expression in the frontal cortex and hippocampus of powdered diet-fed mice were higher and lower in control diet-fed mice, respectively (unpaired *t*-test: $p = 0.0452$, Fig. 9B and $p = 0.003$, Fig. 10B). There were no significant differences in the expressions of DAT in the frontal cortex and hippocampus (unpaired *t*-test: $p = 0.4672$, Fig. 9A and $p = 0.4293$, Fig. 10A).

4. Discussion

The findings of the present study may be summarized as follows: (i) Long-term powdered diet increased the % of open arm time and the total number of arm entries, indicating that the mice have low anxiety, hyperactivity and impulsivity behaviors (EPM test) (Fig. 1), (ii) The % of open arm time in control diet-fed mice was increased by treatment with anxiolytic agent, while the anxiolytic agent did not influence the % of open arm time in powdered diet-fed mice (Fig. 2), (iii) GABA-A receptor antagonist attenuated the increase in the % of open arm time by powdered diet feeding (Fig. 3), (iv) selective DAT inhibitor did not influence the % of open arm time and the total number of arm entries in powdered diet-fed mice. In contrast, the increased the % of open arm time by powdered diet feeding was attenuated by treatment with selective NAT inhibitor, DAT and NAT inhibitor and dopamine D4 receptor agonist (Figs. 4–7), (v) GABA transaminase expressions in the frontal cortex of powdered diet-fed mice were decreased (Fig. 8), (vi) powdered diet feeding induced an increase and a decrease in NAT expression, but not DAT expression, in the frontal cortex and hippocampus, respectively (Figs. 9 and 10). These findings are discussed below.

We have previously reported that mice subjected to long-term feeding on powdered diet exhibits increased SI behavior (Niijima-Yaoita et al., 2013), elevation of blood catecholamine and corticosterone, hyperglycemia, hypertension and no changes in growth curves between diet types; further, we found that among daily dietary habits, mastication of food of adequate hardness is very important for the maintenance of systemic (physical and mental) health (Tsuchiya et al., 2014). Although the SI test has been widely documented as an anxiety test, mainly because of a novel partner/place, the EPM test was also developed to detect anxiety-related behavior. In this study, we chose the EPM test as an approach to study anxiety-related behavior; the long-term powdered diet-fed mice showed an increase in the % of open arm time and total number of arm entries, indicating that the mice subjected to long-term feeding on powdered diet have low anxiety behavior.

It is known that GABA-A receptor plays a critical role in anxiolytic activity and the activation of the GABA-A receptor induced by BZD including diazepam reduces anxiety (for review see Jacob et al., 2008; Möhler et al., 2002). Thus, in this study, to investigate the implication of GABA-A receptor on these behaviors, the effects of diazepam and

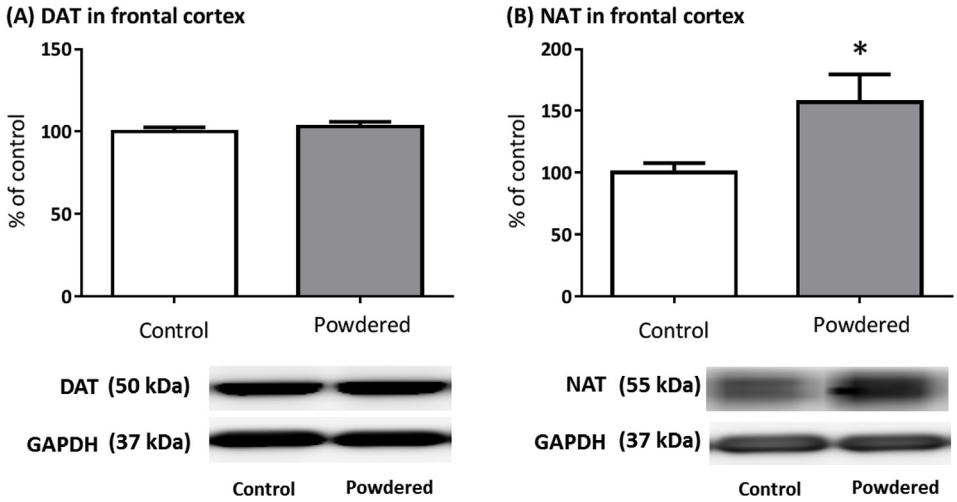

Fig. 9. Influence of powdered diet feeding for 17 weeks on the expression of dopamine transporter (DAT) (A) and noradrenaline transporter (NAT) (B) in the frontal cortex of mice. The data are given as the mean ± SEM for a group of 5 mice/group. *$p < 0.05$; vs. control diet-fed mice (unpaired *t*-test).

bicuculline on the behaviors in powdered diet- and control diet-fed mice, were evaluated. We showed that the increase in the % of open arm time in powdered diet-fed mice was attenuated by treatment with GABA-A receptor antagonist bicuculline, not by treatment with anxiolytic diazepam. However, the % of open arm time in control diet-fed mice was increased by treatment with diazepam. Moreover, both diazepam and bicuculline did not affect the total number of arm entries in powdered diet- and control diet-fed groups. These data indicated that the low anxiety elicited by long-term powderd-diet feeding was mediated via the GABAAergic transmission.

Recent evidence suggests that GABAergic neurotransmission within the medial prefrontal cortex may be central to the regulation of amygdala activity related to emotion and anxiety-related behavior processing (Delli Pizzi et al., 2017). Solati et al. (2013) reported that using rats, bilateral medial prefrontal cortex injection of the GABA-A receptor agonist muscimol produces a low anxiety in the EPM test. Majewska et al. (1986) reported that one of the corticosterone metabolites is allotetrahydrodeoxycorticosterone, a neuroactive 3α 5α-reduced steroid, which are potent positive allosteric modulator of GABA-A receptors. In our previous study, we demonstrated that the plasma corticosterone level of powdered diet-fed mice is higher than that of control diet-fed mice (Tsuchiya et al., 2014), suggesting that the increased corticosterone metabolites may stimulate GABA-A receptor in the powdered diet-fed mice and the low anxiety behavior may be elicited.

Kazi and Oommen (2014) reported that using rats, chronic noise stress induced an increase in GABA levels and a decrease in activity of GABA transaminase in cortex. Moreover, to investigate the relationship between low anxiety behavior elicited by long-term powdered diet feeding and the leading cause of activated GABA-A receptors, we measured the expression of GABA transaminase, GABA metabolic enzymes, in frontal cortex of powdered diet- and control diet-fed mice. In this study, the expression levels of GABA transaminase of the frontal cortex in powdered diet-fed mice were lower than that in control diet-fed mice, indicating that the GABA-A receptor in the frontal cortex of powdered diet-fed mice may be stimulated by an increase in the concentration of GABA via attenuated GABA transaminase.

In our previous study, we proposed that the increase in SI behaviors (i.e. it prolonged SI time) in powdered diet-fed mice might be mediated via alteration of dopaminergic system, especially a decrease in dopamine D4 receptor signals in the frontal cortex (Niijima-Yaoita et al., 2013). Interestingly, dysregulation of dopamine D4 receptor signaling is linked to several pathological conditions, such as ADHD (for review see Rondou et al., 2010). Moreover, the exploratory behavior in open arms may reflect impulsivity for novelty-seeking (for review see Steimer and Driscoll (2003)]. Indeed, the increase in the % of open arm time

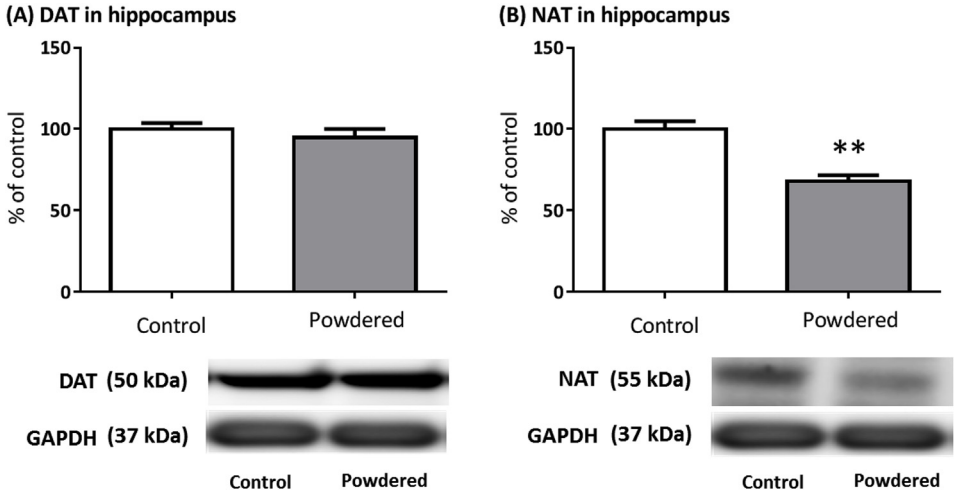

Fig. 10. Influence of powdered diet feeding for 17 weeks on the expression of dopamine transporter (DAT) (A) and noradrenaline transporter (NAT) (B) in the hippocampus of mice. The data are given as the mean ± SEM for a group of 6 mice/group. *$p < 0.05$; vs. control diet-fed mice (unpaired *t*-test).

(low anxiety behavior) and total number of arm entries elicited by powdered diet feeding may relate to the impulsivity and hyperactivity-like symptoms in ADHD, indicating that the long-term powdered diet feeding may increase the risk for the onset of ADHD-like behavior or symptoms.

To investigate the implication of these behaviors in the EPM test on these symptoms in ADHD, we measured whether the ADHD therapeutic agent, methylphenidate and atomoxetine, attenuate the low anxiety or impulsivity-like behavior and hyperactivity-like behavior elicited by powdered diet feeding. In this study, treatments of methylphenidate and atomoxetine improved the impulsivity-like behavior, but not the hyperactivity-like behavior in powdered diet-fed group. Moreover, the % of open arm time and the total number of arm entries in control diet-fed group were not affected by a similar dose of methylphenidate and atomoxetine. Methylphenidate and atomoxetine appear to enhance prefrontal cortex function through inhibition of both DAT and NAT and inhibition of NAT, respectively (for review see Arnsten and Pliszka, 2011). Andrews and Lavin (2006) reported that methylphenidate acts to increase catecholaminergic tone in the prefrontal cortex, and activation of alpha-2 adrenoceptors located in GABA interneurons. Indeed, the inhibition of GABA function may influence the amygdala activity related to emotion and anxiety-related behavior processing and attenuate the low anxiety or impulsivity-like behavior. In this study, we showed an increase in the expression of NAT in the frontal cortex of powdered diet-fed mice. In contrast, DAT expression was not changed in the frontal cortex of powdered diet-fed mice. These findings may suggest the relationship between improvement of methylphenidate and atomoxetine on the low anxiety behavior or impulsive-like behavior elicited by long-term powdered diet feeding and the activation of alpha-2 adrenoceptors by an increase in the concentration of NA mainly via inhibition of NAT in the synaptic cleft. In addition, the involvement of long-term powdered diet feeding on an increased risk ADHD-like behavior onset or symptoms was suggested.

However, in this study, improvement by methylphenidate and atomoxetine on the low anxiety behavior or impulsive-like behavior elicited by long-term powdered diet feeding was not dose dependent. Berridge and Spencer (2016) reported that NA is targeted by pharmacological treatments used to treat prefrontal cortex dysfunction associated with a range of psychopathologies, including ADHD, and modulating the distinct processes via alpha-1 and alpha-2 adrenoceptors, respectively. Moreover, they described that the differential activation of adrenoceptor subtypes within the prefrontal cortex is reflected in the inverted-U shaped function. In addition to the receptor specific actions, the differences of concentration, such as low doses that are within a clinically-relevant range or doses without clinically-relevant range, are reflected in the inverted-U shaped function. These findings may support our data showing that improvements of methylphenidate and atomoxetine were not dose dependent.

Although the low anxiety behavior or impulsive-like behavior in powdered diet-fed mice may be related to changes in noradrenergic functions, i.e., decrease in the concentration of NA in the synaptic cleft via elevated NAT expressions in the frontal cortex, in the previous study we suggested that the powdered diet feeding may cause the increased SI time and the changes in the dopaminergic system, especially the decrease in dopamine D4 receptor signals in the frontal cortex (Niijima-Yaoita et al., 2013). Moreover, in this study, we showed that PD168077, a dopamine D4 receptor agonist, attenuated the low anxiety behavior or impulsive-like behavior in powdered diet-fed mice. In contrast, GBR12909, a DAT inhibitor, which increases the concentration of dopamine in the synaptic cleft, did not influence the low anxiety behavior or impulsive-like behavior in powdered diet-fed mice. Interestingly, agonism of endogenous neurotransmitters at the dopamine D4 receptor has been described not only for dopamine (Asghari et al., 1995), but also for NA and adrenaline (Lanau et al., 1997; Newman-Tancredi et al., 1997). Moreover, it is reported that in the prefrontal cortex, where the DAT density of dopaminergic neurons is low (Sesack et al., 1998), NAT discharges dopamine reuptake (Carboni et al., 1990; Morón et al., 2002). In addition, it is well known that emotional stress induces an elevation of serum glucocorticoids. Ayada et al. (2002) observed that improved mastication behavior might reduce the stress-induced enhancement of serum cortisol. In our previous study, we showed the elevation of serum corticosterone in powdered diet-fed mice (Tsuchiya et al., 2014) and the decrease in the expression of dopamine D4 receptor mRNA, but not in D1, D2, D3 and D5 receptor mRNA in powdered diet-fed mice (Niijima-Yaoita et al., 2013). Barros et al. (2003) reported that corticosterone down-regulates dopamine D4 receptor in a mouse cerebral cortex neuronal cell line. These findings suggest that the masticatory dysfunction induced by long-term powdered diet feeding may cause the low anxiety behavior or impulsive like behavior, the decrease in not only NA but also dopamine in the synaptic cleft of the frontal cortex, and the decreased dopamine D4 receptor signaling via the elevated NAT expression and corticosterone. Indeed, the decreased expression of dopamine D4 receptor may be stimulated by the selective dopamine D4 receptor agonist PD168007, but not by an increase in the concentration of dopamine via inhibition of DAT by GBR12909.

In addition, Shah et al. (2004) reported that using rats, intra-medial prefrontal cortex infusions of the highly selective dopamine D4 receptor antagonist, increased the % of open arm time in the EPM test, indicating low anxiety. Moreover, rodent dopamine D4 receptor activation in prefrontal cortex pyramidal neurons inhibits GABAAnergic functions (Wang et al., 2002). Indeed, the decreased dopamine D4 signals in the frontal cortex of powdered diet-fed mice may attenuate the inhibitory effects of dopamine D4 receptors on GABAAnergic function in regulating amygdala activity related to emotion and anxiety-related behavior processing.

Zhang et al. (2017) reported that chronic social stress up-regulated expression of NAT in the brain is mediated by glucocorticoid receptor (GR) and the GR expressional alterations in response to chronic stress are complex and brain region-specific. However, the measurement of GR protein levels after chronic stress was inconsistent (Kohda et al., 2007; Liberzon et al., 1999; Makino et al., 2002; Trujillo et al., 2016). In this study, we showed the increase and decrease in NAT expressions in the frontal cortex and hippocampus of powdered diet-fed mice, respectively. We previously observed that long-term powdered diet feeding markedly increased the serum level of corticosterone (Tsuchiya et al., 2014). These findings may support the differences in NAT expressions between the frontal cortex and hippocampus in our study.

In conclusion, the present study demonstrated that the dietary habits, e.g. a long-term powdered diet feeding, increased the % of open arm, the total number of arm entries, the expression of NAT, and decrease in expression of GABA transaminase in the frontal cortex. In addition, the increased the % of open arm time in powdered diet-fed mice was attenuated by GABA-A receptor antagonist, ADHD therapeutic agents and selective dopamine D4 receptor agonist, but not by anxiolytic agent or DAT inhibitor. These results suggest that the long-term powdered diet feeding may cause low anxiety or impulsivity, possibly via an increase in NAT expression, decrease in dopamine D4 receptor signals and increase in GABA-A receptor functions in the frontal cortex of mice. Moreover, the long-term powdered diet feeding may increase the risk for onset of ADHD-like behavior or symptoms and the effect of ADHD therapeutic agents on the impulsive behavior might be inhibited mainly by NAT and by the increased NA and/or dopamine levels in the synaptic cleft.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2018.12.002.

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