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ORIGINAL PAPER

Antidepressant-like behavior in brain-specific angiogenesis inhibitor 2-deficient mice

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Abstract Brain-specific angiogenesis inhibitor 2 (BAI2) is a transmembrane protein that is predominantly expressed in the brain. Although BAI2 is supposed to correlate with antiangiogenesis in the brain, its psychiatric function is still unclear. In this study, we examined the influence of BAI2 gene disruption on mood-related behavior using BAI2-deficient mice. BAI2-deficient mice showed significant antidepressant-like behavior in the social defeat test and in the tail suspension test compared with wild-type mice. On the other hand, BAI2-deficient mice had normal basal locomotor activity in the home cage and in the open field test, and normal learning ability and memory retention in the Morris water maze test. Additionally, we found that hippocampal cell proliferation in BAI2-deficient mice was higher than that in wild-type mice. These results indicate that BAI2 has an important role related to depression and influences the hippocampal neurogenesis. BAI2 may be a novel therapeutic target for mood-related disorders.

Keywords BAI2 · Depression · Neurogenesis · Social defeat

Introduction

Brain-specific angiogenesis inhibitor 2 (BAI2) is a transmembrane protein, which is placed in subgroup VII of adhesion-G protein-coupled receptors (GPCRs) based on protein domain analysis [1]. BAI2 is predominantly expressed in the brain, especially at neurons and astrocytes in the hippocampus, the amygdala and the cerebral cortex [2, 3]. Two close homologues, BAI1 and BAI3, have been identified, and all BAIs possess a long N-terminal extracellular region (ECR) that contains thrombospondin type I repeats (TSRs) and a GPCR proteolysis site (GPS) [2, 4]. TSRs are found in several proteins such as thrombospondins, and its physiological functions are related to cell-cell interactions, inhibition of angiogenesis, neurite outgrowth and synaptogenesis [5]. The N-terminal ECR is cleaved at the GPS domain in some adhesion GPCRs [6]. Previously we have reported the possibility that BAI2 is also cleaved at the GPS domain and activates the nuclear factor of activated T-cells (NFAT) pathway in a G protein-dependent manner [7].

BAI2 is considered to have an angiostatic function due to TSRs in the N-terminal ECR because the cleaved N-terminal ECR of BAI1, which contains TSRs, has been reported to inhibit angiogenesis in vivo [8]. Studies using the ischemia brain model in mice and the hypoxic cell culture model of neuroblastoma revealed that the expression levels of BAI2 and vascular endothelial growth factor (VEGF) were inversely correlated [3]. Jeong et al. [9]

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reported that BAI2 may suppress VEGF gene expression by interacting with GA-binding protein (GABP), a transcriptional repressor of VEGF.

In contrast to the investigation of BAI2 regarding an angiostatic factor, its psychiatric functions have not been fully understood. In the public database (Mouse Genome Informatics (MGI) database of the Jackson Laboratory: http://www.informatics.jax.org/), the behavioral analysis data of BAI2-deficient mice in five tests (open field test, tail suspension test, rotarod test, hot plate test and metrazol test) are available; they indicate that BAI2-deficient mice exhibit antidepressant-like behavior in the tail suspension test, but exhibit normal behavior in other tests. In order to clarify the involvement of BAI2 in mood-related behavior, we conducted the social defeat test, which is a well-established test for the analysis of antidepressant-like and anxiolytic behavior, and the tail suspension test using BAI2-deficient mice [10–12]. We also assessed basal locomotor activity in the home cage and in the open field test, and spatial learning and memory in the Morris water maze test, respectively [13, 14]. BAI2-deficient mice showed significant antidepressant-like behavior, but normal basal activity, learning and memory retention. In addition, we investigated the neural mechanism of anti-depressant-like behavior of BAI2-deficient mice. Repeated exposure to social defeat leads to a decrease in hippocampal neurogenesis [15]. It has been proposed that reduced hippocampal neurogenesis plays a causal role in depression, and augmentation of neurogenesis may be important in its remission [16]. We assessed the cell proliferation of dentate gyrus in BAI2-deficient mice by bromodeoxyuridine (BrdU) labeling and immunohistochemical analysis. The cell proliferation in BAI2-deficient mice was significantly higher than that in wild-type mice. These results suggest that BAI2 plays an important role in mood-related behavior, especially in association with hippocampal neurogenesis.

Materials and methods

Animals

Homozygous BAI2-deficient (BAI2−/−) mice were generated from heterozygotes (BAI2+/−) obtained from Deltagen (San Mateo, CA). F1 heterozygous mice were produced as described elsewhere [17]. Briefly, the *bai2* targeting construct, which contains a genomic fragment including the BAI2 protein-coding region partly replaced by an IRES-lacZ-Neo cassette, was electroporated into 129/OlaHsd mouse embryonic stem (ES) cells. Recombinant ES cells were injected into C57BL/6 blastocysts, and male chimeric mice were generated. The chimeric mice were bred with C57BL/6J mice to generate F1 heterozygotes. Homozygotes (KO: BAI2−/−) and wild-type littermates (WT: BAI2+/+) used in this study were 11 to 14 weeks old and weighed 26.8–36.4 g. They were housed in same-sex groups of two to five in a temperature- and humidity-controlled vivarium with food and water ad libitum under a 12-h light/dark cycle (lights on at 0600 h, off at 1800 h). All animal procedures were performed in strict accordance with the guidelines for the Care and Use of Laboratory Animals, Daiichi-Sankyo Co. Ltd.

Social defeat test

To induce social defeat stress, the tested male mice (the 'intruder') were individually placed in the home cage of a highly aggressive resident male mouse (the 'aggressor') in a procedure adapted from a previous study [18]. Specifically, resident Crlj:CD-1(ICR) male mice were housed with normal female partners for more than 5 weeks, and the males that generated pups were selected as the aggressor for the test. Females and pups were removed transiently from the aggressor's cages before starting the social defeat stress procedure, then the intruder mouse was introduced in the aggressor's cage. After recording the latency while the intruder mouse was attacked 20 times by the aggressor mouse (the latency to social defeat), the intruder mouse was returned to his home cage. This procedure was conducted once a day and repeated from days 1 to 5, and days 8 to 12 (day 1 is the first day of the social defeat stress procedure). On day 15, the intruder mouse was introduced in the resident's cage, and after being attacked twice, the intruder mouse was separated from the aggressor mouse by a wire mesh in the same cage. The behavior of the intruder mouse under the social stress condition was recorded for 20 min by an IR beam motion detector (NS-AS01, NeuroScience Inc, Tokyo, Japan) above the cage. The amount of activity was analyzed using a ClockLab system (Actimetrics, Wilmette, IL).

Tail suspension test

A tail suspension test for the antidepressant activity was conducted as described elsewhere [12]. Male mice, isolated visually, were suspended 30 cm above the ground by medical adhesive tape placed 1 cm from the tip of the tail. The immobility time, defined as the absence of limb movement, was recorded using a video camera and analyzed by a highly experienced observer who was blind to the genotype.

Home cage activity test

Male mice were single-housed in the home cages with food and water ad libitum, and after an acclimatization period of 3 days, the activity measurements were performed for 72 h. Movements of the mice were recorded by an infrared sensor (Multi digital 32 port count system, NeuroScience Inc., Tokyo, Japan) throughout the light and dark phases. Cumulative activity measurements in the light and dark phases for 72 h were analyzed.

Open field test

The open field apparatus consisted of a gray plastic chamber (50 × 50 × 15 cm) with a gray floor. The floor of the open field was subdivided into 25 equal squares by 4 × 4 parallel black lines. Behavior was recorded under room light (114 lux at the center of the field) with a video camera mounted above the field. Male mice were placed into the center of the field and observed for 5 min. The following behavioral variables were analyzed: the traveled distance, the number of sections crossed, the number of entries to the center zone (central 30 × 30-cm section of the open field) (center entries), the time spent in the center zone (center time), the number of rearings, the number of groomings and the number of fecal boluses. The traveled distance, the number of sections crossed, center entries and center time were analyzed using an automated tracing device (Etho Vision, Noldus Information Technology Inc, Wageningen, The Netherlands).

Morris water maze

Spatial learning and memory were assessed in the Morris water maze test. The apparatus was a grey polyvinyl-chloride circular pool (148 cm in diameter, 44 cm in height) filled to a depth of 31 cm with water at 17–18°C. An escape platform made of transparent acrylic (12 cm in diameter, 30 cm in height) was placed in a constant position in the pool. The platform was submerged 1 cm below the water surface, and a black stick on the wall of the pool near the platform and a lamp behind the stick were provided as the extra-maze cue. In the training trial, male mice were introduced into the pool facing the wall, and the latency to reach the hidden platform was recorded for up to 90 s. When mice could reach the platform within 90 s and stay on it for more than 30 s, the mice were considered as recognizing the platform and removed from the pool. The training trials were conducted once a day from days 1 to 3 and days 6 to 10 (day 1 is the first day of the training trials). If the mice could not find the platform within 90 s in the day 1 and day 2 trials, they were manually placed onto the platform and permitted to remain there for 30 s. The start location varied among trials. All trials were recorded with a video camera fixed above the center of the pool, and the goal latency and the traveled distance were analyzed using a SMART video-tracking system (Panlab, Barcelona, Spain). On day 11, the mice received a single probe trial. The platform was removed from the pool, and the swimming path of each mouse was recorded over 90 s while they searched for the missing platform. The number of platform crossings was evaluated.

BrdU immunohistochemistry

For labeling dividing cells, such as neural progenitor cells, administration of BrdU and immunohistochemical analysis were performed as described elsewhere [19, 20]. BrdU was dissolved in phosphate-buffered saline and each day administered intraperitoneally for 4 days (100 mg/kg/day). Twenty-four hours after the last administration of BrdU, all mice were deeply anesthetized with sodium pentobarbital and perfusion-fixed by Tissue Fixative (Genostaff, Tokyo, Japan). Brains were removed and immersion-fixed by Tissue Fixative, and then embedded in paraffin by their proprietary procedure. Coronal brain was sectioned at 6 μm between stereotaxic coordinates Bregma −1.0 to −2.0 mm and mounted on slides. Every 5th section was deparaffinized and rehydrated, then antigen retrieval was performed by microwave treatment. Endogenous peroxidase was blocked with 0.3% H_2O_2 in methanol. Immunohistochemistry was performed by using immunhistochemical polymer detection systems (Histofine Mouse Stain Kit; Nichirei Tokyo, Japan). The sections were incubated with mouse monoclonal anti-BrdU antibody (10 μg/ml; Dako, Glostrup, Denmark) at 4°C overnight. The immunoreactive product was visualized by diaminobenzidine and counterstained with hematoxylin (Muto pure chemicals, Tokyo, Japan), and then mounted with Malinol (Muto pure chemicals, Tokyo, Japan). All BrdU-labeled cells in the granule cell layer (GCL) including the subgranular zone (SGZ) were counted at 200× magnification using a light microscope by observers blind to the genotype. The number of BrdU-labeled cells was defined as the total cell counts in five sections per brain and analyzed statistically.

Data analysis

Data were analyzed by a Student's *t* test or Aspin-Welch's *t* test using the SAS preclinical package software version 5.0 (SAS institute Japan, Tokyo, Japan). A two-way ANOVA was performed on the goal latency and the traveled distance data in the Morris water maze learning test to determine whether BAI2-disruption had any effect on

learning. Probability values less than 0.05 ($P < 0.05$) were considered statistically significant. Values are presented as mean ± SEM.

Results

Antidepressant-like behavior in BAI2-deficient mice

BAI2-deficient mice showed antidepressant-like behavior in the social defeat test. The behavioral activity of BAI2-deficient mice under the social stress condition was significantly increased compared to wild-type mice (WT: 417.6 ± 64.5 counts, $N = 10$; KO: 659.2 ± 29.4 counts, $N = 10$; $P < 0.01$, Fig. 1a). The latency to social defeat was not significantly different between the two groups (data not shown). Additionally, we confirmed the antidepressant-like behavior of BAI2-deficient mice in the tail suspension test. The immobility time of BAI2-deficient mice was significantly decreased compared with wild-type mice (WT: 154.2 ± 14.4 s, $N = 10$; KO: 82.1 ± 11.0 s, $N = 10$; $P < 0.01$, Fig. 1b).

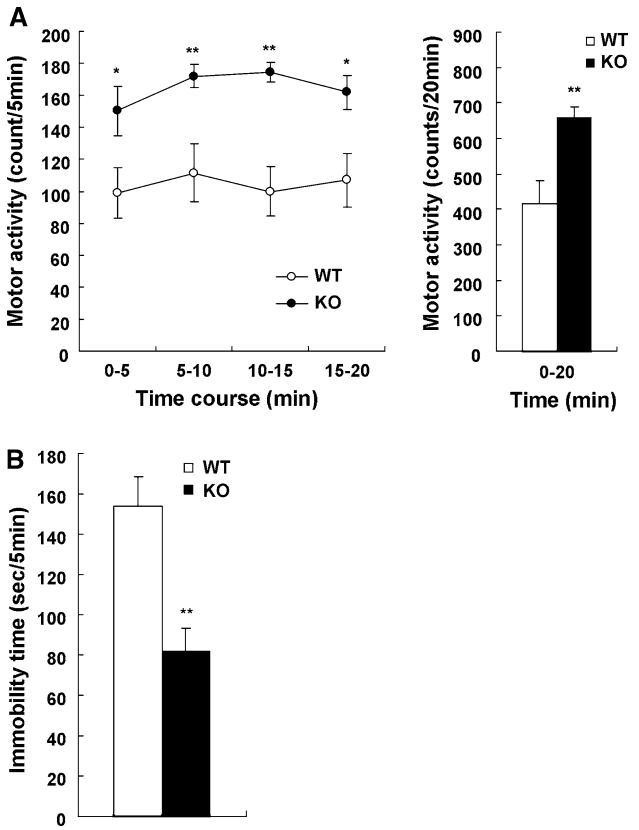

Fig. 1 Antidepressant-like behavior of BAI2-deficient mice in the social defeat test and in the tail suspension test. **a** Motor activity of BAI2-deficient (KO) mice under social defeat stress was significantly increased compared with wild-type (WT) mice (*left* time course, *right* total time). **b** Immobile time of BAI2-deficient (KO) mice during 5 min-test was significantly decreased compared with wild-type (WT) mice in the tail suspension test. Each datum shows the mean ± SEM ($N = 10$). Significant difference from wild-type mice is indicated by a Student's t test or Aspin-Welch's t test (*$P < 0.05$ and **$P < 0.01$)

Normal motor activity in BAI2-deficient mice

In order to examine the basal activity of BAI2-deficient mice, we determined the spontaneous motor activity of mice under nonaversive conditions by analyzing the home cage activity for 72 h (Fig. 2). There was no significant effect of BAI2 gene disruption on the cumulative home cage activity in the light phase (WT: 5,660 ± 489 counts, $N = 10$; KO: 7,540 ± 1,852 counts, $N = 10$; $P = 0.349$) and the dark phase (WT: 15,564 ± 1,233 counts, $N = 10$; KO: 20,125 ± 2,513 counts, $N = 10$; $P = 0.127$) throughout 72 h, although increased motor activity was observed at a few points during the first 24 h (arrows in Fig. 2). Additionally, the motor behavior in a novel environment was assessed in the open field test (Table 1). The number of rearings was significantly decreased in BAI2-deficient mice ($P < 0.01$), but other behaviors did not change (traveled distance $P = 0.826$, sectors crossed $P = 0.662$, center entries, $P = 0.555$, center time $P = 0.989$, the number of groomings $P = 0.232$, the number of fecal boluses $P = 0.657$).

Normal spatial learning ability and memory in BAI2-deficient mice

Spatial learning and memory of BAI2-deficient mice were assessed in a Morris water maze test. In the training trials, the time required to find the submerged platform (goal latency) of BAI2-deficient mice and wild-type mice progressively decreased over the training trials in a similar manner. There was no significant difference between both mice in the goal latency (Fig. 3a). The traveled distance also progressively decreased over the training trials. Although the traveled distance during the training trials of BAI2-deficient mice was longer than that of wild-type mice on some days (days 1, 2, 7), no significant difference was observed at the end of the training trials (days 8, 9, 10) (Fig. 3b). A significant genotype × training trials interaction was not observed in either the goal latency or the traveled distance (goal latency $P = 0.553$, traveled distance $P = 0.276$). The swimming speed of both mice was similar. These results demonstrate that both groups of mice were equally able to learn the location of the platform from cues outside of the pool. In the probe trial, both BAI2-deficient mice and wild-type mice equally crossed over the missing platform. The number of platform crossings was not significantly different between the two groups (Fig. 3c), which shows memory retention was not influenced by BAI2 gene disruption.

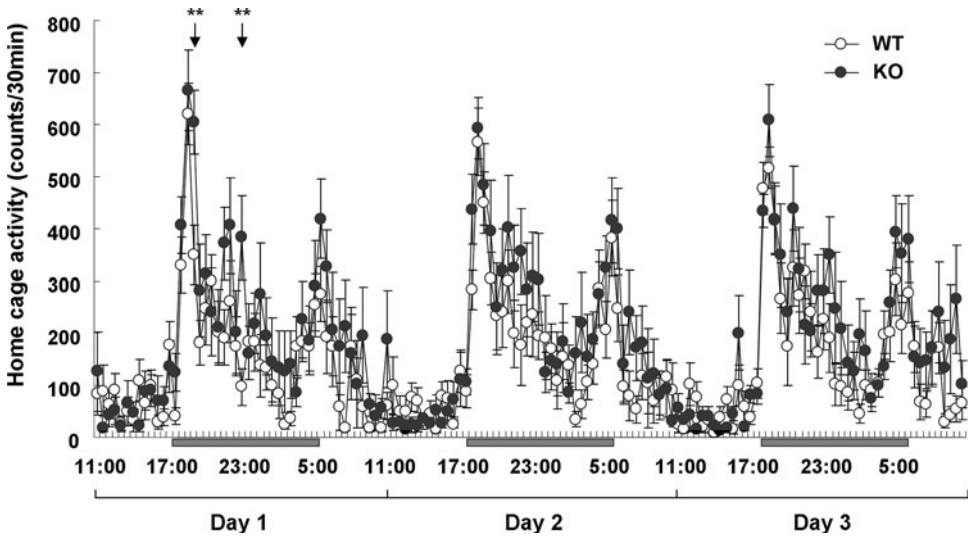

Fig. 2 Home cage activity of wild-type and BAI2-deficient mice. There is no significant difference in the home cage activity between wild-type (WT) and BAI2-deficient (KO) mice, although increased activity was observed at a few points during the first 24 h (*arrow*). Each datum shows the mean ± SEM ($N = 10$). Significant difference from wild-type mice is indicated by a Student's t test or Aspin-Welch's t test (**$P < 0.01$)

Table 1 Locomotor activity of wild-type and BAI2-deficient mice in the open field test

Genotype	Traveled distance (cm)	Sectors crossed (no.)	Center entries (no.)	Center time (s)	Rearing (no.)	Grooming (no.)	Fecal boluses (no.)
WT	2,718.2 ± 190.4	260.3 ± 8.7	24.1 ± 2.1	49.5 ± 6.5	28.4 ± 1.2	0.9 ± 0.2	2.5 ± 0.8
KO	2,669.0 ± 199.2	250.7 ± 19.6	22.1 ± 2.6	49.6 ± 5.3	19.1 ± 2.1**	0.6 ± 0.2	2.0 ± 0.8

Each datum shows the mean ± SEM ($N = 10$). Significant difference from wild-type mice is indicated by a Student's t test (**$P < 0.01$)

Increased hippocampal neurogenesis in BAI2-deficient mice

Neurogenesis in the dentate gyrus of hippocampus is thought to be important for antidepressant-like behavior. We assessed the hippocampal neurogenesis in BAI2-deficient mice by BrdU labeling and immunohistochemical analysis. The number of BrdU-labeled cells in the GCL of BAI2-deficient mice was significantly higher than that of wild-type mice (WT: 79.6 ± 14.8, $N = 5$; KO: 102.0 ± 15.0, $N = 5$; 28% increase; $P < 0.05$, Fig. 4b).

Discussion

BAI2 is predominantly expressed at neurons and astrocytes in the brain. However, its psychiatric function has not been elucidated yet. In this study, we examined the influence of BAI2 gene disruption on mood-related behavior using BAI2-deficient mice in the social defeat test and in the tail suspension test. The social defeat test provides a more naturalistic model of social stress characterized by aggressive interactions that are intense, unpredictable, and inescapable. Repeated social defeat causes an increase in depressive behavior, and this effect is recovered by chronic administration of antidepressants [21]. We also confirmed the recovery effect of milnacipran, a serotonin noradrenaline reuptake inhibitor, on depressive behavior of defeated mice in the social defeat test (data not shown). The tail suspension test is a well-established model for the analysis of depressive behavior and is often used to screen antidepressants in mice [12]. We demonstrated that BAI2-deficient mice showed significant resistance to depression after the repeated stress in the social defeat test. We also confirmed that BAI2-deficient mice showed significantly reduced immobile time in the tail suspension test compared with wild-type mice. On the other hand, BAI2-deficient mice had normal basal activity in the home cage, and normal learning ability and memory retention in the Morris water maze test. Also in the open field test, the behaviors correlated with basal locomotor activity, including the traveled distance and the number of the sectors crossed, were normal. These results indicate that the antidepressant-like behavior of BAI2-deficient mice is not due to an abnormality in the locomotor activity, learning and memory.

Rearing behavior in the open field test is considered to reflect both exploratory activity and emotionality [22]. In this study, BAI2-deficient mice showed significantly reduced rearing behavior in the open field test. However, other behaviors correlated with exploratory activity and emotionality, including the center time and the center entries, were not different between wild-type and BAI2-deficient mice. Additionally, from the results in the public database (MGI), behaviors of BAI2-deficient mice in the open field test, including the center time, were normal. Therefore, we think that exploratory activity and emotionality of BAI2-deficient

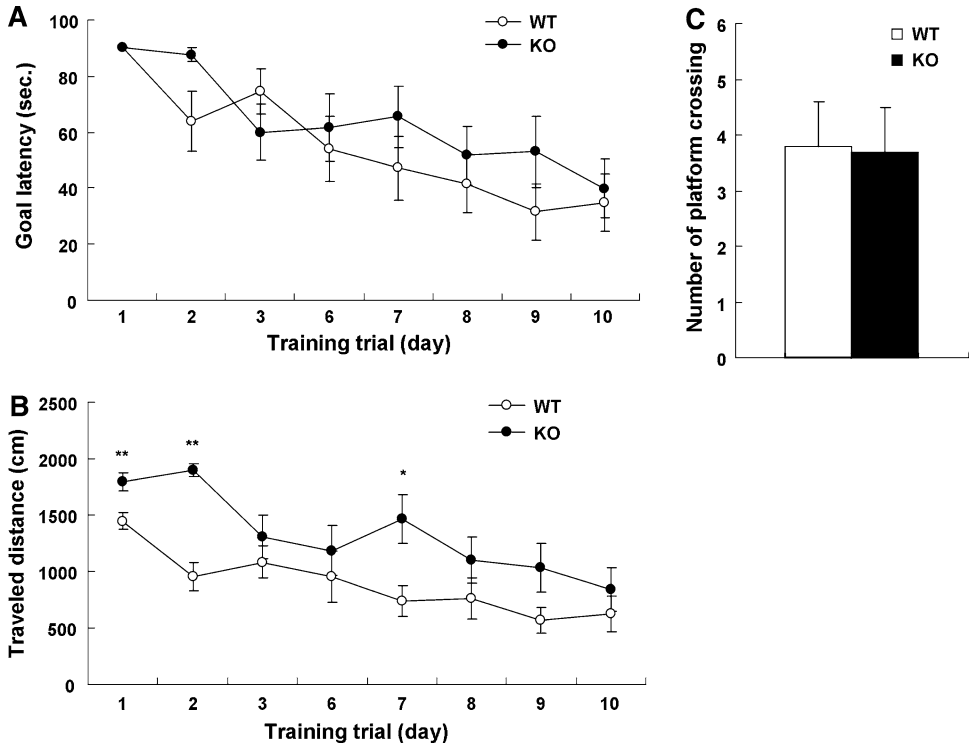

Fig. 3 Normal learning ability and memory retention of BAI2-deficient mice in the Morris water maze. **a** The time required to find the submerged platform (goal latency) of wild-type (WT) and BAI2-deficient (KO) mice was recorded during the training trials in the Morris water maze test. No significant difference was observed between the two groups. **b** Although the traveled distance during the training trials of BAI2-deficient mice was longer than that of wild-type mice on some days (days 1, 2, 7), no significant difference was observed at the end of the training trials (days 8, 9, 10). **c** The number of platform crossings was recorded over 90 s in the probe trial. No significant difference was observed between the two groups. Each datum shows shows the mean ± SEM ($N = 10$). Significant difference from wild-type mice is indicated by a Student's t test or Aspin-Welch's t test ($^*P < 0.05$ and $^{**}P < 0.01$)

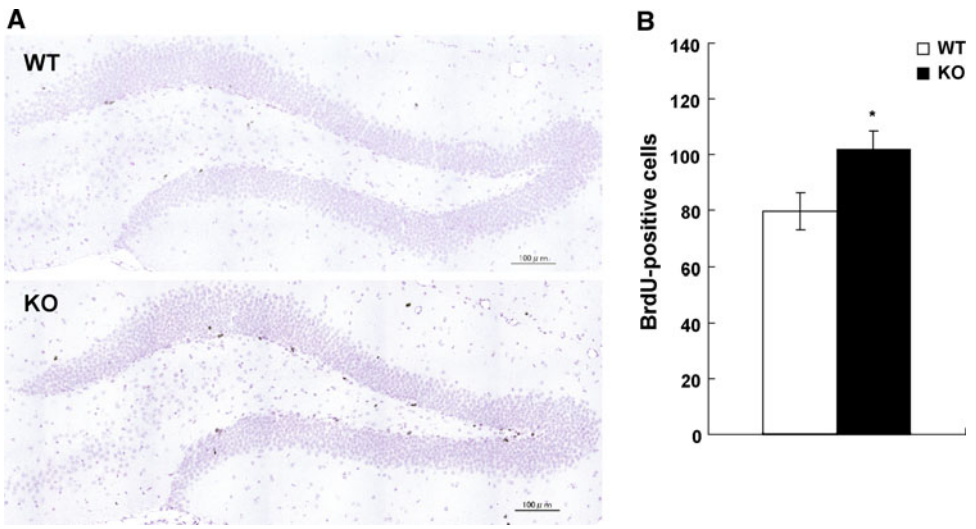

Fig. 4 Increased hippocampal neurogenesis in BAI2-deficient mice. BAI2-deficient mice received injections of BrdU for 4 days, and hippocampal tissue sections were stained with anti-BrdU antibody. **a** Representative photomicrographs (×200 magnification) from wild-type (WT) and BAI2-deficient (KO) mice and **b** the number of BrdU-positive cells in the GCL including the SGZ, defined as the total cell counts in five sections, are presented. Each datum shows mean ± SEM ($N = 5$). Significant difference from wild-type mice is indicated by a Student's t test ($^*P < 0.05$)

mice are not affected severely. Further investigation with other behavioral tests, such as the elevated plus maze test or the light/dark exploratory test, could be useful for analyzing more clearly the effect of BAI2 gene disruption on exploratory activity and emotionality.

Neurogenesis in the adult hippocampus is closely related to stress. Stress significantly downregulates neurogenesis in adult hippocampus, and chronic treatment with antidepressant upregulates it [23–25]. Several growth factors, including fibroblast growth factor-2 (FGF-2), brain-derived neurotrophic factor (BDNF) and VEGF, also stimulate neurogenesis, and they exert antidepressant effects [15, 16, 26, 27]. Recently, a leading hypothesis of depression suggests that neurotrophic factors and adult neurogenesis play critical roles in mediating the behavioral response to antidepressants [16, 25]. We confirmed that the cell proliferation in the dentate gyrus in BAI2-deficient mice was significantly higher than that in wild-type mice. Although we did not examine the detailed localization of BAI2 in the dentate gyrus, it was reported that BAI2 is highly expressed at neurons in the GCL of the hippocampal dentate gyrus [3]. BAI2 is also reported to suppress the expression of VEGF through the interaction with GABP in vitro [9]. Warner-Schmidt and Duman [27] demonstrated that VEGF infusions mimic the action of antidepressants in rats, and it is an essential mediator for the behavioral action of antidepressants. We consider that enhanced neurogenesis in the hippocampus plays a critical role for the antidepressant-like behavior in BAI2-deficient mice, and it may result from increased expression of VEGF in the brain.

Previously, we reported the possibility that the N-terminal ECR of BAI2 containing TSRs is cleaved at the GPS domain [7]. Because the cleaved N-terminal ECR of BAI1 containing the TSRs, which is called vasculostatin, can suppress vascularization, it is possible that the N-terminal ECR of BAI2 also has an angiostatic function [8]. It was reported that the TSRs of thrombospondin-1 interact with CD36, a cell surface receptor on microvascular endothelial cells, and then inhibit the migration of endothelial cells [28]. Therefore, the ECR of BAI2 may similarly bind to CD36 and may contribute to the antiangiogenic activity of BAI2. Angiogenesis in the hippocampus is stimulated by antidepressant treatments including electroconvulsive seizures, and the treatment of corticosterone that induces a depression-like behavior in rats markedly inhibits endothelial cell proliferation in the hippocampus and the prefrontal cortex [25, 29]. Adult hippocampal neurogenesis has been described to occur in the angiogenic niche [30, 31]. It is our speculation that BAI2 gene disruption promotes the angiogenic and neurogenic niche, which enhances neurogenesis in the hippocampus.

In summary, we demonstrated that BAI2 plays an important role in psychiatric functions from the results of antidepressant-like behaviors and increased hippocampal neurogenesis in BAI2-deficient mice. Although further investigations are needed to clarify the underlying mechanism, BAI2 will likely be a novel therapeutic target for mood-related disorders.

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Conflict of interest The authors declare no conflict of interest.

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