

# Vexin is upregulated in cerebral cortical neurons by brain-derived neurotrophic factor

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## Abstract

**Aim:** Chromosome 8 open reading frame 46 (C8orf46), a human protein-coding gene, has recently been named Vexin. A recent study indicated that Vexin is involved in embryonic neurogenesis. Additionally, some transcriptomic studies detected changes in the mRNA levels of patients with psychiatric and neurological diseases. In our previous study, we sought for target genes of brain-derived neurotrophic factor (BDNF) in cultured rat cortical neurons, finding that BDNF potentially leads to the upregulation of Vexin mRNA. However, its underlying mechanisms are unknown. In the present study, we assessed the regulatory mechanisms of the BDNF-induced gene expression of Vexin in vitro.

**Methods:** We reanalyzed ChIP-seq data in various human organs provided by the ENCODE project, evaluating acetylation levels of the 27th lysine residue of the histone H3 (H3K27ac) at the Vexin locus. The transcriptomic effects of BDNF on rat Vexin (RGD1561849) were evaluated by real-time quantitative PCR (RT-qPCR) in primary cultures of cerebral cortical neurons, in the presence or absence of inhibitors for signaling molecules activated by BDNF.

**Results:** The Vexin locus and its promoter region in the brain angular gyrus show higher acetylation levels of the H3K27 than those in other organs. Stimulation of cultured rat cortical neurons, but not astrocyte, with BDNF, led to marked elevations in the mRNA levels of Vexin, which was inhibited in the presence of K252a and U0126.

**Conclusion:** The upregulated H3K27ac in the brain may be associated with the enriched gene expression of Vexin in the brain. It is indicated that BDNF induces the gene expression of Vexin in the cortical neurons via the TrkB-MEK signaling pathway.

## KEYWORDS

brain-derived neurotrophic factor, cultured cortical neurons, H3K27ac, Vexin

Koshimizu and Suzuki contributed equally to this study.

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## 1 | INTRODUCTION

Chromosome 8 open reading frame 46 (C8orf46), or Vexin, is a protein-coding gene in human encoding for 207 amino acids. The rat RNA-seq transcriptomic BodyMap database, which catalogs the expression profiles of gene and transcripts in various organs, shows that Vexin is highly expressed in the brain.<sup>1</sup> It is also demonstrated in the Allen Brain Atlas (<http://mouse.brain-map.org/>) that the mRNA of mouse Vexin (3110035E14Rik) is distributed in the cerebral cortex and hippocampus regions. Some transcriptomic studies have detected changes in the mRNA levels of Vexin in relation to psychiatric and neurological disorders, such as schizophrenia<sup>2,3</sup> and Huntington's disease.<sup>4</sup> These observations indicate that Vexin may play a role in the central nervous system (CNS). Recently, Moore et al<sup>5</sup> reported that Vexin could be involved in the regulation of neuroregeneration in the frog embryo, which, to the best of our knowledge, is currently the only study that has assessed the molecular functions of Vexin.

The brain-derived neurotrophic factor (BDNF) is a member of a family of neurotrophins that play a pivotal role in neuronal differentiation, structure, and function (Hempstead 2015). We have investigated molecules whose gene expression is regulated by BDNF in cerebral cortical neurons<sup>6,7</sup> to understand the overall regulation of BDNF-dependent neuronal differentiation through gene regulatory networks. Our preliminary RNA-seq analysis on BDNF-stimulated cultured rat cerebral cortical neurons indicates that BDNF could lead to the upregulation of the mRNA of rat Vexin, formerly termed RGD1561849 (unpublished data). The objectives of the present study were to reveal whether and how BDNF regulates the expression of Vexin in cortical neurons.

## 2 | METHODS

Chromatin immunoprecipitation sequencing (ChIP-seq) data generated by the Encyclopedia of DNA Elements (ENCODE) project<sup>8</sup> were obtained at the Gene Expression Omnibus (GEO) database. The following data were used: brain (GSM1112807), thyroid gland (GSM2700584), liver (GSM1112808), uterus (GSM2698835), and pancreas (GSM2700597). The data H3K27ac ChIP-seq tracks for Vexin (hg19, chr8:67, 403, 491-67, 432, 759) were visualized using the Integrative Genomics Viewer<sup>9</sup>.

Wistar rats (strain Slc: W; RRID: RGD\_2314928) were sourced from Nippon SLC (Hamamatsu, Japan). All efforts were made to minimize animal suffering and the number of animals used for the studies. Animals were housed, handled, and bred according to the Fundamental Guidelines for Proper Conduct of Animal Experiment and Related Activities in Academic Research Institutions by Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan. Recombinant human BDNF was kindly provided by Sumitomo Pharmaceuticals (Osaka, Japan) and was dissolved in 2% bovine serum albumin (BSA)/phosphate-buffered saline (PBS). The final solvent concentration in the culture medium was 0.01%. K252a,

LY294002, and U0126 were dissolved in dimethyl sulfoxide (DMSO), and the final solvent concentrations were 0.02%, 0.1%, and 0.1%, respectively.

Primary cultures of dissociated cerebral cortical neurons were prepared from the rats (both sexes) at embryonic day 20 (E20). The animals were exposed to isoflurane in the air until they became unconscious. The anesthetized state of the rats was confirmed by the disappearance of the eyelid reflex, corneal reflex, and loss of muscular tone. The animals were then immediately sacrificed by cervical dislocation, followed by decapitation, to ensure minimal suffering of the animals. The neurons were cultured in a serum-free Neurobasal Medium (Gibco) containing B27 supplement (Gibco) at a final density of  $2 \times 10^6$  cells on 6-well plates coated with polyethylenimine (PEI) for the real-time quantitative polymerase chain reaction (RT-qPCR) assay. Cultures were incubated in medium containing  $1 \mu\text{M}$  cytosine arabinoside (AraC) to suppress glial growth after 3 days in vitro (DIV3). BDNF was applied at DIV6 or DIV7. Transfection was carried out using Lipofectamine 2000 (Invitrogen) in the Opti-Minimal Essential Medium (MEM) medium (Invitrogen), according to the manufacturer's instructions. Imaging or cell fixation was carried out 24 hours after gene transfection. Astrocyte pure cultures were prepared as previously described.<sup>6</sup> Briefly, primary cultures of astrocytes were prepared from the cerebral cortex of neonatal Wistar rats. Astrocytes were maintained in 75-cm<sup>2</sup> flasks in a Minimum Essential Medium (MEM)-based growth medium containing 100  $\mu\text{g/L}$  epidermal growth factor (EGF) (Gibco), 20 mM glucose, 25 mM NaHCO<sub>3</sub>, 5% fetal bovine serum (FBS), and 0.5 mM glutamine. After the astrocytes became confluent (10-14 days), cells were harvested and replated on 35-mm dishes. When 70%-80% confluency was reached, the medium was replaced with a fresh medium without EGF for 48 hours before BDNF treatment.

Real-time quantitative PCR (RT-qPCR) was performed as described previously.<sup>6</sup> Briefly, the total RNA was purified from cultures using an RNeasy Mini Kit (Qiagen) and then amplified using the ABI StepOnePlus RT-PCR (Applied Biosystems) and One-Step SYBR PrimeScript RT-PCR Kit II (Takara Bio) with the following primer sets: Vexin (forward, 5'-CAGTGATGAGAATATTGAAGTTTTCAC-3'; reverse, 5'-AGCTCTTGACTCTTCTCCTGGAC-3') and GAPDH (used as a housekeeping gene; forward, 5'-TGCACCACCAACTGCTTAG-3'; reverse, 5'-GGATGCAGGGATGATGTTTC-3').<sup>10</sup> Analyses of the PCR amplifications were carried out using StepOnePlus RT-PCR (Applied Biosystems). To confirm the amplification specificity, we subjected PCR products to a dissociation curve analysis and gel electrophoresis on a 2% agarose gel to ensure the melting temperature and size of the DNA fragment. Expression levels for each mRNA were estimated by normalization to GAPDH levels measured in the same samples.

Significance was analyzed using a one-way or two-way analysis of variance (ANOVA). Post hoc comparison of means was carried out with Tukey's HSD test for multiple comparisons when appropriate. Statistical analysis was carried out using R-software (version 3.6.3). A *p*-value of .05 or less was considered statistically significant. The data were expressed as the means  $\pm$  standard error of the mean

(SEM). All experiments were performed at least twice to confirm their reproducibility. The authors were not blinded to the results, and no randomization was performed. Representative results from single experiments are presented in the figures.

### 3 | RESULTS AND DISCUSSION

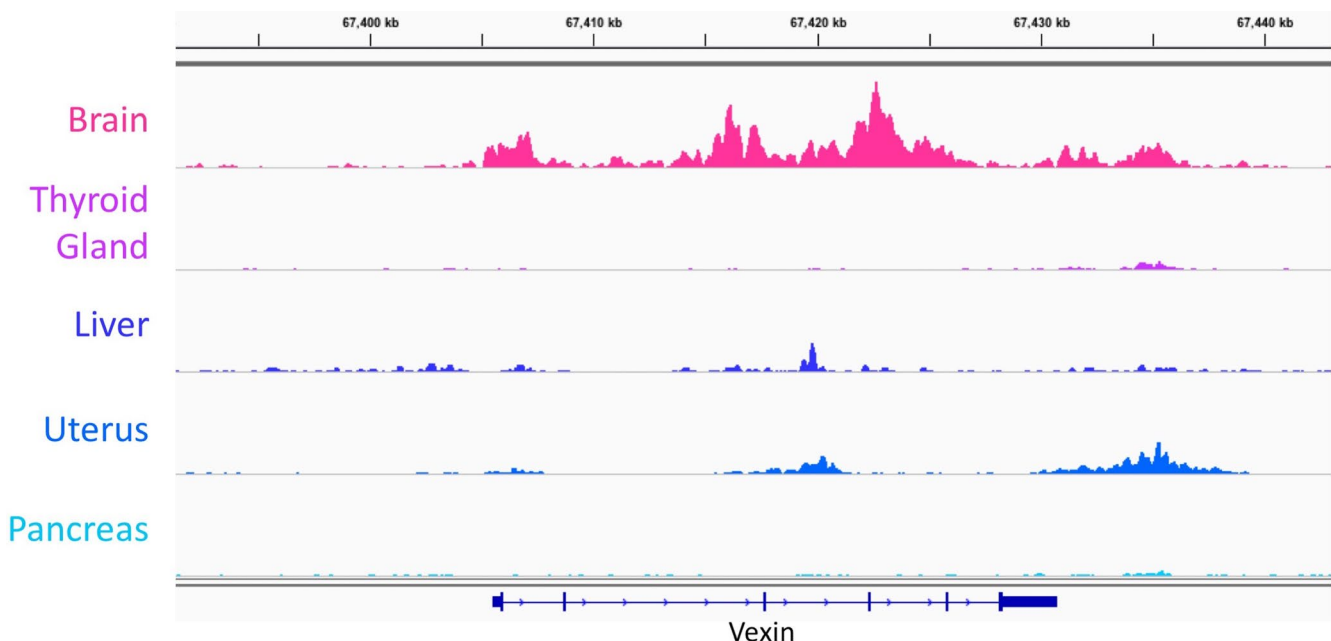
We first assessed where the transcription of the Vexin gene is activated by the epigenetic regulation in several human tissues. Acetylation of H3K27 (H3K27ac) is known to activate transcription by facilitating DNA unwinding and increasing accessibility to transcriptional factors.<sup>11</sup> Therefore, we examined the levels of H3K27ac at the Vexin locus in various human tissues, by reanalyzing publicly available chromatin ChIP-seq data provided by the ENCODE project.<sup>8</sup> H3K27ac ChIP-seq tracks were visualized with the Integrative Genomics Viewer<sup>9</sup> in Figure 1. H3K27ac levels at the Vexin locus (hg19, chr8:67,403,491-67,432,759) and its promoter region (hg19, chr8:67,405,435-67,407,235; annotated by Ensembl) were distinctively higher in the brain angular gyrus compared with other tissues, the thyroid gland, liver, uterus, and pancreas. These data are consistent with a previous report that indicated the abundant expression of Vexin in the brain.<sup>1</sup>

Next, we assessed the expression levels of Vexin in human and rat brains at various developmental stages, using publicly available transcriptome data sets. In the human brain (GSE11512),<sup>12</sup> the expression levels of Vexin increased over time, peaking at the age of 20 years, before subsequently decreasing with aging (Figure 2A). Consistent with this observation, expression levels of Vexin

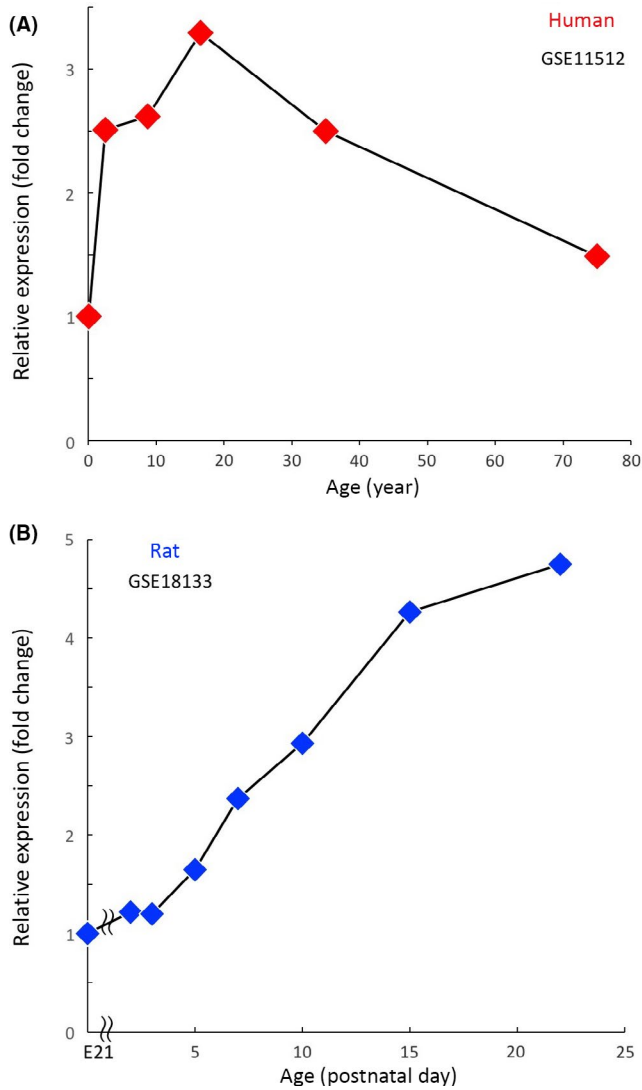
(RGD1561849) also increased over time during the postnatal developmental stage of rat brains (GSE18133)<sup>13</sup> (Figure 2B). These observations indicate the possibility that Vexin plays a molecular role in the brain during the developmental and maturational stages.

BDNF is also known to have important functions in the maturing brain. We therefore evaluated whether the gene expression of Vexin is regulated by BDNF in cells cultured from rat cortex. Primary cerebral cortical cultures were treated with 100 ng/mL BDNF for 3 days, and gene expression levels were measured by RT-qPCR (Figure 3A). The results indicated that BDNF significantly enhanced the gene expression of Vexin in the cerebral culture (BDNF-treated:  $7.25 \pm 1.26$ , Control:  $1.00 \pm 0.08$ ;  $P < .01$ ). In the culture system, we have previously reported over 90% MAP-2-positive neurons, while glial fibrillary acidic protein (GFAP)-positive astrocytes and oligodendrocyte marker O4-positive oligodendrocytes accounted for only 5.4% and 0.2%, respectively.<sup>10</sup>

We have previously demonstrated that BDNF led to the phosphorylation of TrkB in this culture system.<sup>7</sup> We next assessed whether TrkB is involved in the BDNF-induced upregulation of Vexin mRNA in cerebral cortical cultures, using K252a, a Trk receptor inhibitor. Cortical cultures were treated with 100 ng/mL BDNF in the presence or absence of 200 nM K252a for 3 days. In our previous study, we confirmed that K252a inhibits the BDNF-induced phosphorylation of TrkB using the same conditions.<sup>14</sup> BDNF-induced Vexin mRNA upregulation (BDNF-treated:  $8.19 \pm 0.59$ , Control:  $1.00 \pm 0.05$ ; Tukey's HSD post hoc test,  $P < .001$ ) was significantly inhibited in the presence of K252a (BDNF- and K252a-treated:  $1.88 \pm 0.11$ , Tukey's HSD post hoc test,  $P < .05$ , compared with K252a-treated:  $0.45 \pm 0.02$ ; Tukey's HSD post hoc test,  $P < .001$ ,



**FIGURE 1** Acetylation at the 27th lysine residue of the histone H3 protein (H3K27ac) in the Vexin locus in various human tissues was assessed using published ChIP-seq data provided by the ENCODE project. Levels of the acetylation at the 27th lysine residue of the H3K27ac at the Vexin locus and its neighboring region in the brain angular gyrus (GSM1112807) compared with other tissues, the thyroid gland (GSM2700584), liver (GSM1112808), uterus (GSM2698835), and pancreas (GSM2700597) were indicated. ChIP-seq data provided by the ENCODE project were reanalyzed, and H3K27ac ChIP-seq tracks were visualized using the Integrative Genomics Viewer (IGV)



**FIGURE 2** Ontogeny of Vexin mRNA in human and rat brains. Publicly available transcriptome data sets for (A) human Vexin (C8orf46; GSE11512) and (B) rat Vexin (RGD1561849; GSE18133) were reanalyzed. The expression levels of Vexin mRNA are plotted

compared with BDNF-treated; two-way ANOVA interaction effect,  $F_{1,16} = 92.7$ ;  $P < .001$ ; Figure 3B). These observations indicate that BDNF induced Vexin gene expression in the cerebral cortical neurons in a TrkB-dependent manner.

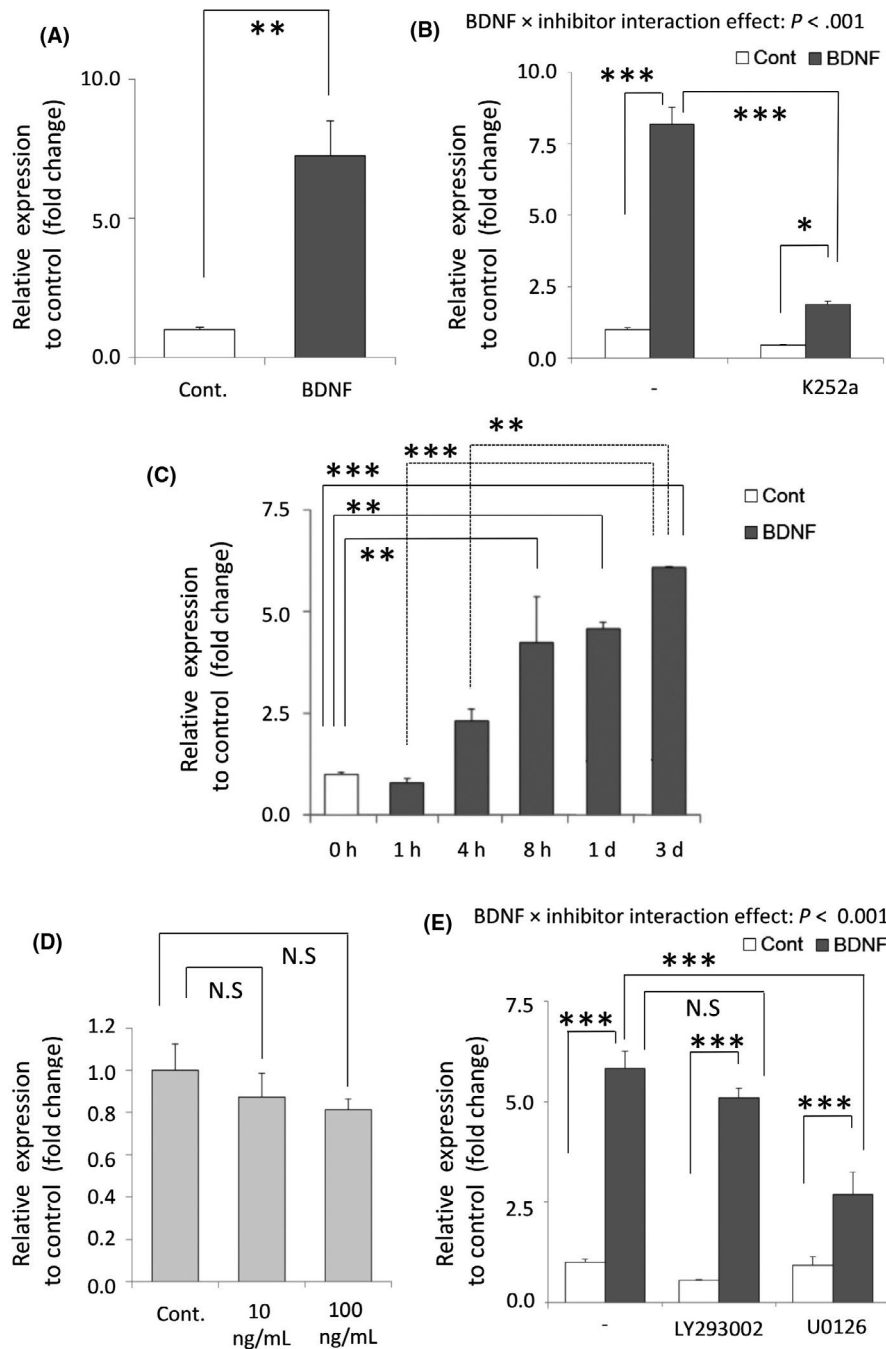
We also assessed the time course of the BDNF-induced upregulation of Vexin mRNA. The cultures were treated with 100 ng/mL BDNF for 1 hour, 4 hours, 8 hours, 1 day, and 3 days. Gene expression levels were measured by RT-qPCR (Figure 3C). No significant upregulations were detected 1 hour (BDNF-treated:  $0.78 \pm 0.12$ , Control:  $1.00 \pm 0.04$ ; Tukey's HSD post hoc test,  $P > .05$ ) and 4 hours (BDNF-treated:  $2.30 \pm 0.30$ ; Tukey's HSD post hoc test,  $P > .05$ ) after the BDNF treatment, but there were significant enhancements in the gene expression of Vexin 8 hours (BDNF-treated:  $4.23 \pm 1.13$ ; Tukey's HSD post hoc test,  $P < .01$ ), 1 day (BDNF-treated:  $4.57 \pm 0.15$ ; Tukey's HSD post hoc test,  $P < .01$ ), and 3 days (BDNF-treated:  $6.08 \pm 0.01$ ; Tukey's HSD post hoc

test,  $P < .001$ ) after the treatment. The gene expression of Vexin at 3 days after the treatment was significantly higher than that of 1 hour (Tukey's HSD post hoc test,  $P < .001$ ) and 4 hours (Tukey's HSD post hoc test,  $P < .01$ ).

To assess whether there is any cell specificity for the BDNF-induced upregulation of Vexin, the astrocyte cultures were stimulated with 100 ng/mL of BDNF, and the levels of Vexin mRNA were measured after 3 days of treatment. BDNF treatment led to no significant changes in Vexin gene expression in the astrocytes (10 ng/mL BDNF-treated:  $0.87 \pm 0.11$ , Tukey's HSD post hoc test,  $P > .05$ , compared with Control:  $1.00 \pm 0.12$ ; 100 ng/mL BDNF-treated:  $0.81 \pm 0.05$ , Tukey's HSD post hoc test,  $P > .05$ , compared with Control). This indicates that BDNF upregulated Vexin mRNA in cells other than astrocytes, presumably in neuronal cells (Figure 3D).

Next, we sought TrkB's downstream signaling molecules that are involved in the BDNF-induced upregulation of Vexin. Cortical cultures were treated over 3 days with 100 ng/mL BDNF in the presence or absence of LY294002 (10  $\mu$ M), an inhibitor of phosphoinositide 3-kinase (PI3K), or U0126 (10  $\mu$ M), an inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK). Then, the amount of Vexin mRNA was measured (Figure 3E). Two-way ANOVA detected a significant interaction effect between BDNF stimulation and inhibitor treatment ( $F_{2,12} = 13.96$ ;  $P < .001$ ). The BDNF-induced Vexin upregulation (BDNF-treated:  $5.83 \pm 0.43$ , Control:  $1.00 \pm 0.08$ ; Tukey's HSD post hoc test,  $P < .001$ ) did not change in the presence of LY294002 (BDNF- and LY294002-treated:  $5.10 \pm 0.23$ , LY294002-treated:  $0.55 \pm 0.03$ ; Tukey's HSD post hoc test,  $P < .001$ ). There was no significant difference between BDNF-treated cells and BDNF- and LY294002-treated cells (Tukey's HSD post hoc test,  $P > .05$ ). On the other hand, the BDNF-induced Vexin upregulation was partially, but significantly, inhibited by U0126 (BDNF- and U0126-treated:  $2.68 \pm 0.57$ , U0126-treated:  $0.93 \pm 0.22$ ; Tukey's HSD post hoc test,  $P < .001$ ). There was a significant difference between BDNF-treated cells and BDNF- and U0126-treated cells (Tukey's HSD post hoc test,  $P < .001$ ). These findings indicate that MEK positively regulates the BDNF-induced gene expression of Vexin.

Our in vitro assay thus identified the signal molecules that are involved in the BDNF-dependent Vexin gene expression, namely TrkB and MEK. On the other hand, LY294002, an inhibitor for PI3K, failed to attenuate the BDNF-induced upregulation of Vexin mRNA. Therefore, it is likely that the PI3K pathway is not responsible for BDNF-induced Vexin upregulation. The enhanced H3K27ac in the brain may be associated with the enriched gene expression of Vexin in the brain. It remains unclear as to whether the upregulated H3K27ac is involved in the BDNF-induced gene expression of Vexin in neurons. This is, to the best of our knowledge, the first study to examine the underlying molecular mechanism of the gene expression of Vexin in the CNS. Biochemical and physiological analyses are required to further elucidate the molecular functions and their underlying mechanisms of Vexin in the cerebral cortical neurons.



**FIGURE 3** Brain-derived neurotrophic factor (BDNF) treatment enhanced the gene expressions of Vexin in rat cerebral cortical neuronal cultures. (A) Primary cultures of rat cerebral cortical neurons were treated with or without BDNF (100 ng/mL) for 3 d, and expression levels of Vexin mRNA were measured using real-time quantitative polymerase chain reaction (RT-qPCR). \*\* $P < .01$ , Student's *t* test,  $n = 3$  independent culture dishes. (B) Primary cultures of rat cerebral cortical neurons were treated with BDNF (0, 100 ng/mL) for 3 d in the presence or absence of 200 nM K252a, and expression levels of Vexin mRNA were measured by RT-qPCR. \* $P < .05$ , \*\*\* $P < .001$ , Tukey's HSD post hoc test,  $n = 5$  independent culture dishes. (C) The cortical cultures were treated with BDNF (100 ng/mL), and the gene expression levels of Vexin mRNA were assessed by RT-qPCR 0 h, 1 h, 4 h, 8 h, 1 d, and 3 d after the BDNF treatment. \* $P < .05$ , \*\* $P < .01$ , \*\*\* $P < .001$ , Tukey's HSD post hoc test,  $n = 3$  independent culture dishes. (D) The astrocyte cultures were stimulated with 100 ng/mL of BDNF. The levels of Vexin mRNA were measured by RT-qPCR after 3 d of treatment. NS: not significant, Tukey's HSD post hoc test,  $n = 4$  independent culture dishes. (E) Cortical cultures were treated with 100 ng/mL BDNF in the presence or absence of inhibitors PI3K (LY294002, 10  $\mu$ M) or MEK (U0126, 10  $\mu$ M) for 3 d. The expression levels of Vexin mRNA were measured by RT-qPCR. NS: not significant, \*\*\* $P < .001$ , Tukey's HSD post hoc test,  $n = 3$  independent culture dishes



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## CONFLICT OF INTEREST

None.

## AUTHOR CONTRIBUTION

HK, SS, NA, and HM participated in research design. HK, SS, AK, RM, KO, TM, NA, and HM conducted experiments and performed data analysis. HK, SS, NA, and HM wrote or contributed to the writing of the manuscript.

## DATA REPOSITORY

The data that support the findings of this study are available in the Supplemental Data 1 of this article.

## ANIMAL STUDIES

All animal experiments were conducted in strict accordance with the protocols set out by the Institutional Animal Care and Use Committee of Kagawa University.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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