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Deficiency of WFS1 leads to the impairment of AVP secretion under dehydration in male mice

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Abstract

Wolfram syndrome (WS) is mainly caused by mutations in the *WFS1* gene and characterized by diabetes mellitus, optic atrophy, hearing loss, and central diabetes insipidus (CDI). WFS1 is an endoplasmic reticulum (ER)-resident transmembrane protein, and *Wfs1* knockout (*Wfs1*−/−) mice, which have been used as a mouse model for WS, reportedly manifested impairment of glucose tolerance due to pancreatic β-cell loss. In the present study, we examined water balance, arginine vasopressin (AVP) secretion, and ER stress in AVP neurons of the hypothalamus in *Wfs1*−/− mice. There were no differences in urine volumes between *Wfs1*−/− and wild-type mice with free access to water. Conversely, when mice were subjected to intermittent water deprivation (WD) for 20 weeks, during which water was unavailable for 2 days a week, urine volumes were larger in *Wfs1*−/− mice, accompanied by lower urine AVP concentrations and urine osmolality, compared to wild-type mice. The mRNA expression of immunoglobulin heavy chain binding protein, a marker of ER stress, was significantly increased in the supraoptic nucleus and paraventricular nuclei in *Wfs1*−/− mice compared to wild-type mice after WD. Our results thus showed that *Wfs1* knockout leads to a decrease in AVP secretion during dehydration, which could explain in part the mechanisms by which *Wfs1* mutations cause CDI in humans.

Keywords Diabetes insipidus · Arginine vasopressin · Wolfram syndrome · Endoplasmic reticulum stress · BiP

Introduction

The endoplasmic reticulum (ER) is an essential cellular organelle and is responsible for the posttranslational modification and proper folding of membrane and secretory proteins. ER stress occurs when the demand for protein synthesis exceeds the protein folding capacity. Excessive ER stress results in cellular dysfunction or cell death, and it has been implicated in the pathogenesis of various endocrine or neurodegenerative disorders [1, 2]. The unfolded protein response (UPR) is an adaptive cellular response that ameliorates ER function and prevents ER stress-induced cell death. This is mediated by 3 transmembrane proteins: inositol requiring 1 (IRE1), double-stranded-RNA-dependent protein kinase-like ER kinase (PERK), and activating transcription factor 6 (ATF6). The immunoglobulin heavy chain binding protein (BiP) works as a chaperone and suppresses these signaling pathways under basal conditions; when ER stress occurs, these 3 signaling pathways are activated by dissociation of BiP. Among these signaling pathways, ATF6α is known to upregulate *BiP* mRNA expression, leading to enhanced protein folding capacity [3–5].

Arginine vasopressin (AVP) is an antidiuretic hormone that is mainly synthesized in the supraoptic nucleus (SON) and paraventricular nuclei in the hypothalamus (PVN) [6]. We previously showed that *BiP* mRNA was highly expressed in AVP neurons even under basal conditions [7], suggesting that AVP neurons are exposed to ER stress to meet the demand for AVP synthesis and secretion for the maintenance

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of water balance. Central diabetes insipidus (CDI) is a disorder resulting from a deficiency of AVP and characterized by polyuria and polydipsia. While most causes of CDI are acquired, there is a subclass called familial neurohypophysial diabetes insipidus (FNDI) in which polyuria manifests several months or years after birth [8, 9]. Previous studies including ours showed that excessive ER stress is a pathogenetic cause of the impairment of AVP secretion and cell death of AVP neurons in rodent models of FNDI [9–13].

Wolfram syndrome (WS) is a rare autosomal recessive disorder characterized by early-onset diabetes mellitus, progressive optic atrophy, deafness, and CDI [14, 15]. WS is mostly caused by mutations of *Wfs1* gene, encoding the ER-resident transmembrane protein wolframin (WFS1) [14, 16], which has been shown to play a key role in maintaining ER homeostasis [17–19]. Diabetes mellitus and optic atrophy are common clinical manifestations in WS, and they usually occur in the first decade [20]. On the other hand, CDI in WS usually occurs around the second or third decade, and its incidence is reported to range from 30 to 87% [21–23]. Previous studies reported that *Wfs1* knockout animals recaptured the phenotype of diabetes mellitus in patients with WS, and that ER stress induced by *Wfs1* knockout caused the dysfunction of β-cells [24–26].

In the present study, we examined water balance, AVP secretion, and ER stress in AVP neurons of the hypothalamus in *Wfs1*−/− mice in order to clarify the underlying mechanisms by which CDI manifests in WS.

Materials and methods

Animals

Wfs1−/− mice were generated previously [24]. The strain was produced by intercrossing male and female heterozygotes (*Wfs1*+/−), and their wild-type (*Wfs1*+/+) littermates were used as control. Animal care and use were performed in accordance with the institutional guidelines. Animal experiments were performed according to procedures approved by the Animal Experimentation Committee of the Nagoya University Graduate School of Medicine. Mice were maintained in a room with controlled temperature on a 12-h/12-h light–dark cycle (23.0 ± 0.5 °C, lights on 09:00 to 21:00).

Measurement of urine volume, urine AVP concentration, and urine osmolality

Two-month-old male mice were divided into 2 groups; one group had free access to water and the other was subjected to intermittent water deprivation (WD), which consisted of repeated cycles of continuous WD for 48 h followed by 5 days with free access to water, as reported previously [10]. Mice were housed in metabolic cages, and the 24-h pooled urine was collected for 20 weeks. In the intermittent WD group, urine volume was measured on the first day during WD, or on days 4 and 5 after WD (Supplemental Fig. 1). Urine AVP concentrations were measured by radioimmunoassay (AVP kit Yamasa; Yamasa Corporation, Chiba, Japan). Urine osmolality was determined by the cryoscopic method (Oriental Yeast Co., Ltd., Tokyo, Japan).

Measurement of food intake, body weight, and blood glucose concentration

Food intake and body weight were measured every week for 28 weeks. 5 days after the 20th intermittent WD, blood samples were taken by tail bleeding at the beginning of the light cycle between 09:00 and 10:00 in 28-week-old mice, and blood glucose concentrations were measured using a glucometer (Medisafe Mini; Terumo, Tokyo, Japan).

Immunohistochemistry

Immunohistochemistry was performed as described previously [10, 27–29]. Briefly, mice were transcardially perfused, and the brains were fixed with 4% paraformaldehyde and cut into 50-μm coronal sections using a vibratome (VT1200 S; Leica Biosystems, Wetzlar, Germany). After the sections were washed and blocked, they were incubated with primary antibodies overnight at 4 °C. The slices were rinsed and then incubated with secondary antibodies for 2 h at RT. Images were captured by a fluorescence microscope (BZ-9000; Keyence, Osaka, Japan) and processed using Adobe Photoshop CS5 software (Adobe Systems, San Jose, CA, USA). Neurons were counted from the matched slices at 0.7 and 0.82 mm caudal from bregma for the SON and PVN, respectively [29].

Antibodies

The primary antibodies used in this study were as follows: rabbit anti-WFS1 (1:200) [24, 30], guinea pig anti-AVP (1:2000; T-5048; Peninsula, San Diego, CA, USA), and mouse anti-neurophysin I [OT-NP; 1:100; PS38; kindly provided by Dr. Harold Gainer, National Institutes of Health (NIH), Bethesda, MD, USA] [31, 32]. The secondary antibodies used in this study were as follows: Alexa Fluor 488-conjugated goat anti-mouse IgG (H + L) highly cross-adsorbed (1:1000; A11029; Invitrogen, San Diego, CA, USA), Cy3-conjugated affinipure donkey anti-guinea pig IgG (H + L) (1:500; 706-165-148; Jackson ImmunoResearch, West Grove, PA, USA), and Alexa Fluor 647-conjugated donkey anti-rabbit IgG (H + L) highly cross-adsorbed (1:1000; A31573; Invitrogen).

In situ hybridization

In situ hybridization were performed as reported previously [7, 10, 27–29]. Briefly, brains were cut into 16-µm coronal sections on a cryostat at − 20 °C, thaw-mounted on Superfrost Plus microscope slides (Matsunami Glass Ind., Osaka, Japan), and stored at − 80 °C. The matched slices at 0.70 mm (SON) and 0.82 mm (PVN) caudal from bregma from each mouse were examined. The probes for *Avp* and *Bip* mRNA were radiolabeled with [^{35}S] UTP and [^{35}S] CTP (PerkinElmer Life Sciences, Waltham, MA, USA). After the procedures of prehybridization, hybridization, and posthybridization, the sections were exposed to Bio-Max MR film (Carestream Health, Rochester, NY, USA) for 7 h *(Avp* mRNA) or 48 h (*Bip* mRNA). The expression levels of mRNA were quantified by measuring of the integrated optimal densities of the images, and expressed in arbitrary units (AU) using ImageJ software (NIH).

Statistical analysis

Statistical analysis was performed by unpaired t test, one-way ANOVA, or two-way ANOVA, with repeated measures followed by the Bonferroni test as appropriate. Data are shown as mean ± SE. Values of $P < 0.05$ were considered statistically significant.

Results

WFS1 is expressed in AVP neurons in the hypothalamus

Immunohistochemistry using specific anti-WFS1 antibody revealed that WFS1 proteins were expressed in the SON and PVN in wild-type (WT) mice, and colocalized with AVP and oxytocin (Fig. 1). The quantitative analyses revealed that 95.9% (658/686) AVP neurons and 89.1% (303/340) oxytocin neurons were WFS1-positive. Conversely, WFS1 proteins were not expressed in AVP neurons in the SON or PVN in *Wfs1*−/− mice (Supplemental Fig. 2).

Increased urine volume and decreased AVP secretion in *Wfs1*−/− mice during WD

There were no significant differences in urine volume or water intake for 20 weeks between *Wfs1*−/− and WT mice with access to water ad libitum (Fig. 2a, b). There were also no significant differences in urine volume or water intake between genotypes for 20 weeks when measured on days 4 and 5 after 2 day-WD every week (Fig. 2c, d). However, urine volume was significantly greater in *Wfs1*−/− than in WT mice when measured during 20th WD, but not during 1st or 12th WD (Fig. 2e). The urine AVP concentration as well as urine osmolality was significantly lower in *Wfs1*−/− than in WT mice during 20th WD (Fig. 2f, g).

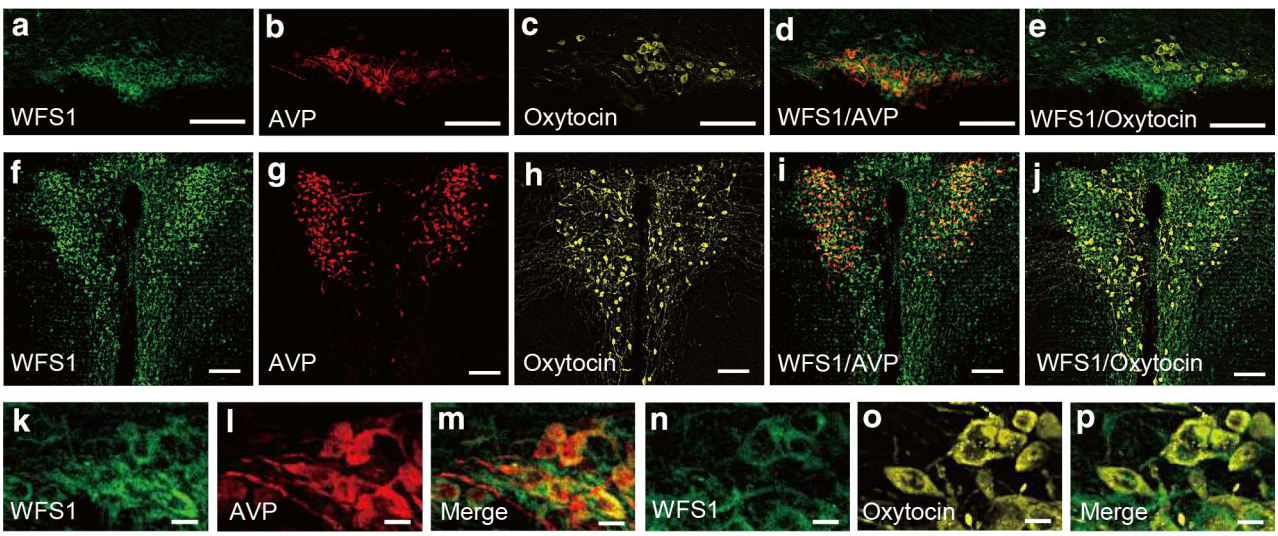

Fig. 1 WFS1 is expressed in AVP neurons in the hypothalamus. Immunofluorescence staining for WFS1 (green), AVP (red), and oxytocin (yellow) in the SON (**a**–**e** and **k**–**p**) and PVN (**f**–**j**) of 2-month-old WT mice. Lower magnification images staining for WFS1 (**a** and **f**), AVP (**b** and **g**), and oxytocin (**c** and **h**). **d** and **i** are merged images of staining for WFS1 and AVP. **e** and **j** are merged images of staining for WFS1 and oxytocin. Higher magnification images staining for WFS1 (**k** and **n**), AVP (**l**), and oxytocin (**o**). **m** and **p** are merged images of staining for WFS1 and AVP, WFS1 and oxytocin, respectively. Scale bars, 100 µm (**a**–**j**), 10 µm (**k**–**p**)

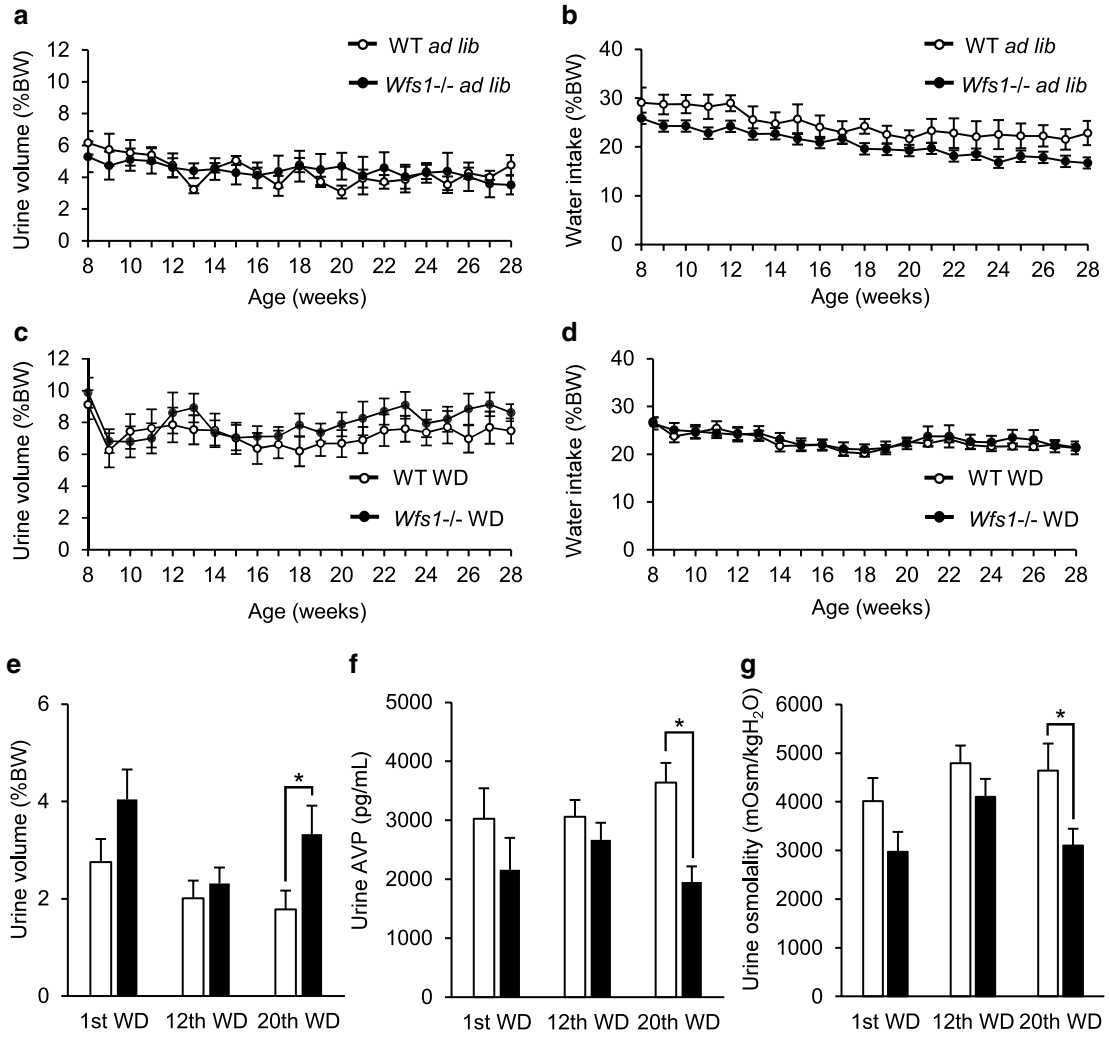

Fig. 2 Increased urine volume and decreased AVP secretion in *Wfs1*−/− mice during WD. Urine volume (**a**) and water intake (**b**) in WT (○) and *Wfs1*−/− mice (●) with water access ad libitum. Mean urine volume (**c**) and water intake (**d**) measured 4 and 5 days after each WD in WT (○) and *Wfs1*−/− mice (●) subjected to intermittent WD. Urine volume (**e**), urine AVP concentration (**f**), and urine osmolality (**g**) in WT (white bars) and *Wfs1*−/− mice (black bars) during the 1st, 12th, and 20th WD. Results are expressed as mean ± S.E. n = 4 animals per group with water access ad libitum, 7–8 animals per group subjected to intermittent WD. *P < 0.05, compared to WT mice during WD. % BW percentage body weight

Knockout of *Wfs1* increases the expression of BiP in response to WD

AVP mRNA expression levels in the SON and PVN were not significantly different under basal conditions between *Wfs1*−/− and WT mice (data not shown); they also did not significantly differ between genotypes after 1st (data not shown) or 20th WD (Fig. 3a–c). However, while there was no significant difference in *BiP* mRNA expression levels in the SON and PVN under basal conditions between genotypes (data not shown), the levels were significantly increased in *Wfs1*−/− than in WT mice after 1st (data not shown) and 20th WD (Fig. 3D-F).

Food intake, body weight, and blood glucose concentration

There were no significant differences in food intake or body weight for 20 weeks between *Wfs1*−/− and WT mice with access to water ad libitum or subjected to intermittent WD (data not shown). There were no significant differences in blood glucose concentrations (*Wfs1*−/− 147.00 ± 7.86 mg/dL vs WT 157.63 ± 6.20 mg/dL) between genotypes in 28-week-old mice subjected to intermittent WD. These data suggest knockout of *Wfs1* did not affect energy homeostasis or glucose metabolism in the current study.

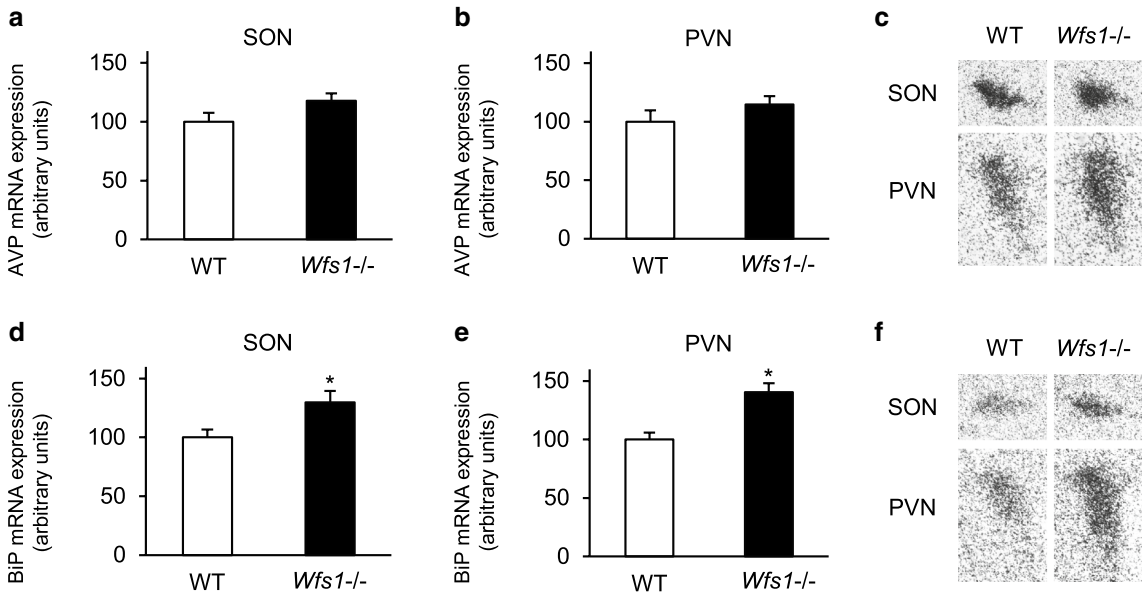

Fig. 3 Knockout of *Wfs1* increases the expression of BiP in response to WD. Expression of *AVP* (**a**, **b**) and *BiP* (**d**, **e**) mRNA in the SON and PVN in WT (white bars) and *Wfs1*−/− mice (black bars) after intermittent WD for 20 weeks. Representative images of in situ hybridization for *AVP* (**c**) and *BiP* (**f**) mRNA. Mean expression levels of *AVP* and *BiP* mRNA in WT mice are expressed as 100. Results are expressed as mean ± SE. n = 6–8 animals per group. *P < 0.05, compared to WT mice

Discussion

In the present study, we demonstrated that WFS1 is expressed in AVP neurons in the SON and PVN of WT mice, and that the urine volume was larger after repeated WD in *Wfs1*−/− mice, which was accompanied by a lower urine AVP concentration and lower urine osmolality, compared to WT mice. To the best of our knowledge, this is the first study to show the impairment of AVP secretion in WS model animals.

Previous studies showed that both *Wfs1* mRNA and proteins were expressed in the SON and PVN [33–35]. In the current study, we not only confirmed but also extended these findings by showing that WFS1 is localized in both AVP and oxytocin neurons in the SON and PVN.

A previous report indicated that plasma insulin levels did not decrease until 36 weeks after birth in *Wfs1*−/− mice [24]. While hyperglycemia due to insulin deficiency could cause osmotic diuresis, it is not the case in the current study, as we observed urine volume and water intake in *Wfs1*−/− mice from 8 to 28 weeks after birth.

FNDI model mice manifest increases in urine volume even with ad libitum access to water [9, 10]. Compared to FNDI model mice, the phenotype of *Wfs1*−/− mice with respect to water balance was mild. This is consistent with the clinical manifestation: patients with FNDI develop progressive polyuria several months or years after birth [36], while those with WS develop CDI, which is sometimes partial, in the second or third decade of life [21].

WFS1 plays important roles in regulating ER function, cytoplasmic calcium homeostasis [19], mitochondrial function [19], and UPR activation [18]. It has been reported that *Wfs1* knockout animals show increased BiP expression in the pancreas, retina, and brainstem [24, 25, 37, 38]. In this study, we showed that *BiP* mRNA expression was increased in AVP neurons of *Wfs1*−/− mice compared to WT mice after WD. Elevated BiP expression might reflect ER stress in AVP neurons, as BiP has been used as a marker of ER stress [39, 40]. Alternatively, BiP upregulation might result from activated ATF6α signaling due to knockout of WFS1, as a previous study using pancreatic β-cell lines showed that WFS1 downregulates ATF6α by the ubiquitin–proteasome pathway, and that knockdown of WFS1 induced an increase in the expression of ATF6α and BiP [18]. We previously reported that upregulation of BiP in the AVP neurons under dehydration was abolished in ATF6α knockout mice [28]. In any case, a relatively mild phenotype of *Wfs1*−/− mice in water balance might be due to the increased expression of BiP, given that BiP plays a protective role in AVP neurons [27]. It is also of note that, while urine AVP concentrations were lower after WD in *Wfs1*−/− mice than in WT mice, there were no differences in *AVP* mRNA in the SON and PVN between genotypes. These data suggest the possibility that knockout of *Wfs1* affected AVP neurons at the post-translational level.

There are a few limitations in this study. First, we chose male mice for analysis based on a previous study showing that the phenotype of diabetes mellitus in *Wfs1* knockout mice was more evident in male than in female mice [24]. However, it is possible that the phenotypes could be prominent in females, as in the case of FNDI mice [9]. Second, although it is likely that knockout of *Wfs1* induced ER stress and affected intracellular trafficking at the level of the ER, we have not examined the morphology of the ER in AVP neurons by electron microscopy.

In conclusion, we showed that *Wfs1* knockout mice manifested decreases in AVP secretion during dehydration, which was accompanied by increased BiP expression in AVP neurons.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11102-021-01135-6.

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Author contributions HT and HA designed the project. JK and HT performed the experiments and analyzed the data with technical help and advice from TM, YH, YK, DH, HS, TK, MS, TO, YI, SI, RB, and KT. JK, HT, KT, YT, and HA wrote the manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

Ethical approval All procedures were approved by the Animal Experimentation Committee of the Nagoya University Graduate School of Medicine, and performed in accordance with the institutional guidelines for animal care and use.

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