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ARTICLE

Melatonin ameliorates hypertension in hypertensive pregnant mice and suppresses the hypertension-induced decrease in Ca^{2+}-activated K^+ channels in uterine arteries

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Abstract

Decreased secretion of melatonin was reported to be associated with an enhanced risk of hypertension and diabetes. However, the effect of melatonin on gestational hypertension (GH) and the underlying mechanism remain unclear. A GH mouse model was established via electrical stimulation. The hypertensive phenotypes were indicated by systolic blood pressure (SBP) and urinary protein levels. Uterine artery (UtA) endothelial function was detected by relaxation, peak systolic velocity (PSV), end-diastolic velocity (EDV), resistance index (RI) and pulsatility index (PI). Protein expression levels were determined using immunochemistry and Western blots. Pregnancy outcomes were indicated by the fetal live ratio, fetal weight and placental weight. Melatonin supplementation ameliorated hypertensive phenotypes in the mice with GH and enhanced UtA endothelial response to acetylcholine. The BK_{Ca} potassium channel was involved in the effect of melatonin on UtA endothelial function, and melatonin promoted BK_{Ca} potassium channel expression and function in UtAs. Finally, melatonin improved pregnancy outcomes in pregnant mice. In conclusion, melatonin ameliorates hypertension in hypertensive pregnant mice and suppresses hypertension-induced decreases in Ca^{2+}-activated K^+ channels in uterine arteries.

Keywords Melatonin · Hypertension · K^+ channel · Uterine arteries

Introduction

Gestational hypertension (GH) is a condition that develops during the pregnancy period and is defined as hypertension at a gestational age of 20 weeks or longer (middle or late pregnancy) [1]. GH is one of the main causes of mortality and morbidity for fetuses and mothers worldwide [2, 3]. Approximately 5–7% of all pregnancies are complicated by GH [4]. Women with GH are at a high risk of renal dysfunction, placental abruption, subsequent cardiovascular morbidity and cesarean delivery [5–7]. GH development initiates with a normal pregnancy process but eventually leads to severe health problems of fetuses and mothers by altering vascular function, morphology, and endothelial barrier integrity and by affecting endothelium-dependent vasodilation in mesenteric arteries of aged offspring [7–10]. Statistical analysis indicated that women with a history of GH more frequently develop higher low-density lipoprotein cholesterol, long-term endothelial dysfunction and higher blood pressure than those without a history of GH [11]. More importantly, GH development commonly results in complications in the heart, brain and kidneys, which is a severe threat to maternal and fetal health [11]. Therefore, it is urgent to develop strategies for more effective treatment of GH.

Melatonin is a pineal gland hormone secreted at night and plays an important role in various physiological functions, such as circadian rhythm mediation, energy balance regulation, reproductive control, epigenetic regulation, amelioration of chronic kidney disease by targeting the renin-angiotensin system, and attenuation of renal sympathetic overactivity and reactive oxygen species in neurogenic hypertension [12–18].

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However, melatonin could also be secreted by the placenta during pregnancy, and the pineal gland is not the only origin [19]. Preeclampsia, another type of pregnancy-induced hypertension, leads to reduced placenta secretion of melatonin and modified expression of melatonin receptor, eventually resulting in melatonin deficiency during pregnancy [20]. In addition, the reduced secretion of melatonin during pregnancy increases the risk of GH development and diabetes [21]. Dexamethasone-induced programmed hypertension in pregnant rats could be attenuated by maternal melatonin therapy by changing renin-angiotensin system components, modulating histone deacetylase expression and restoring nephron numbers [22]. In the L-NLG-nitro-l-arginine methyl ester-induced GH rat model, melatonin administration attenuated oxidative stress, urine protein content and blood pressure and recovered the fetal weight and fetal live ratio [23], indicating the protective effects of melatonin against GH.

In this study, we aimed to investigate the effect of melatonin on mice with GH and tried to discover the underlying mechanism. We found that melatonin supplementation ameliorated hypertensive phenotypes in mice with GH, enhanced UtA endothelial response to acetylcholine (Ach), and improved pregnancy outcomes in pregnant mice. Mechanistically, the BK_{Ca} potassium channel was involved in the effect of melatonin on UtA endothelial function, and melatonin promoted BK_{Ca} potassium channel expression and function in UtAs. Our study indicated that melatonin ameliorated hypertension in hypertensive pregnant mice and suppressed hypertension-induced decreases in Ca^{2+}-activated K^+ channels in uterine arteries.

Methods

GH model

C57BL/c mice were randomly divided into 6 groups: the wild-type (WT), wild-type+melatonin (10 mg/kg/day), model (GH)+melatonin 5 (5 mg/kg/day), model (GH)+melatonin 10 (10 mg/kg/day), model (GH)+melatonin 15 (15 mg/kg/day) and amlodipine (5 mg/kg/day) groups. Twelve mice were used in each group.

The GH mouse model was induced via electrical stimulation as described previously [24]. Briefly, male and female mice were kept in the same cage. After pregnancy, the mice were placed in a cage (22 cm × 22 cm × 28 cm) with a grid floor and subjected to electric foot shocks, which could be used to mimic maternal stress [25]. The delivery of intermittent electric shocks (60–80 V, 20 ms in duration) through the grid floor every 2–30 s was randomly controlled by a computer. Stimulation was performed once a day at the soles of mice for 3 h. After 14 days of continuous stimulation, the mice were believed to develop GH. The study was approved by the ethics committee of Zibo Central Hospital (2019–127).

On GD (gestational day) 12.5, melatonin supplementation was performed via oral gavage at different doses (5 mg/kg/day, 10 mg/kg/day, or 15 mg/kg/day) for different groups. Amlodipine and apocynin (4′-hydroxy-3′-methoxyacetophenone) (Sigma-Aldrich, St Louis, MO, USA) dissolved in 0.5% carboxymethylcellulose-Na solution were administered to mice at 5 mg/kg/day. Melatonin supplementation was continuously carried out for 7 days.

Systolic blood pressure (SBP)

On GD 17.5, the SBP of different groups of WT mice (control and melatonin 10) and GH model (control, melatonin 5, melatonin 10, and melatonin 15) mice was detected in a quiet facility by tail-cuff plethysmography (Visitech 2000 system). The first 10 recordings of the measurement of blood pressure were discarded to acclimatize the mice to the 37 °C warm platform. Then, 30 recordings of blood pressure were taken for each mouse. The mean of 30 recordings was recorded.

Urinary protein levels

The urine of different groups of WT mice (control and melatonin 10) and GH model (control, melatonin 5, melatonin 10, and melatonin 15) mice was collected on GD17.5. The urinary protein concentrations (mg/ml) were detected using a commercial bicinchoninic acid (BCA) protein assay kit (Thermo Fisher Scientific, Waltham, MA, 23225) following the manufacturer's instructions. The total urinary protein per day (mg/day) was the sum of 5 detections measured at 5 different time points.

UtA vascular function

The UtAs of different groups of WT mice (control and melatonin 10) and GH model (control, melatonin 5, melatonin 10, and melatonin 15) mice were collected on GD18.5. The surrounding adipose tissue of UtAs was cleaned using physiologic salt solution (PSS; in mM, 117 NaCl, 25 $NaHCO_3$, 4.69 KCl, 2.4 $MgSO_4$, 1.6 $CaCl_2$, 1.18 KH_2PO_4, 6.05 glucose, 0.034 EDTA; pH 7.4) on ice. The artery segments were fixed on 40 μm steel wires of the myograph chamber, followed by immersion in PSS solution at 37 °C that was gassed using 5% CO_2, 20% oxygen and 75% nitrogen. Then, the arteries were normalized using 0.9 luminal pressure $(L)_{13.3}$ kPa.

After equilibration for 20 min, the arteries were exposed to two polarizing solutions (KPSS; 120 mM KCl in PSS, equimolar substitution of KCl for NaCl). Then, the arteries were washed using PSS. The concentration-response curve to U46619 (thromboxane mimetic, 10^{-10}–2×10^{-6} M, Cayman

Chemicals) was obtained and used to calculate the EC_{80} concentration of U46619. Endothelium-dependent relaxation to ACh (10^{-12}–10^{-4} M) was assessed in arteries pre-constricted with an EC_{80} dose of U46619.

Hemodynamic parameter detection

WT mice (control and melatonin 10) and GH model (control, melatonin 5, melatonin 10, and melatonin 15) mice were anesthetized on GD18.5. The MS 550D probe (VisualSonics; 22–55 MHz, 15 mm maximum depth of penetration, 14.08 mm maximum width) was used for scans. Doppler waveforms of UtAs were obtained from both proximal and internal iliac arteries.

Peak systolic velocity (PSV) was defined as the highest point of the systolic waveform. End diastolic velocity (EDV) was defined as the end point of the diastolic waveform. The resistance index (RI) was calculated using RI = (PSV-EDV)/PSV. The pulsatility index (PI) was calculated using PI = (PSV-EDV)/mean velocity.

Western blot

UtA from different groups of mice was collected and lysed. Then, samples with 20 μg proteins were loaded on 10% polyacrylamide and eclectically separated. Then, the proteins were transferred onto polyvinylidene difluoride membranes, followed by blocking with 5% nonfat milk. The membranes were incubated with primary antibody against BK_{Ca} channel β1 subunits (Santa Cruz Biotechnology, Santa Cruz, CA). Then, the membranes were incubated with secondary horseradish peroxidase-conjugated antibodies. The signals were visualized with enhanced chemiluminescence reagents.

Immunochemistry

UtAs from different groups of mice were collected and snap frozen using liquid nitrogen. The frozen tissues were cut into sections of 5 μm thickness and then fixed for 10 min using acetone, followed by air drying for 1 h at room temperature. The primary antibody against BK_{Ca} channel β1 subunits (Santa Cruz Biotechnology, Santa Cruz, CA) was used for incubation for 1 h at room temperature. The EnVisionTM Detection System (Dako, Germany) was used to stain the sections.

Statistical analysis

All data are shown as the mean ± standard deviation (SD). Significant differences between groups were detected by one- or two-way ANOVA and a post hoc test. $P < 0.05$ was considered significant.

Results

Maternal melatonin supplementation ameliorated hypertensive phenotypes in pregnant mice

We first investigated the effect of melatonin in the established GH mouse model and in WT mice. The SBP in the mice with GH was significantly increased compared with that in the control group of WT mice, indicating the establishment of a GH mouse model. Supplementation with melatonin at doses of 5, 10 and 15 mg/kg/day significantly suppressed SBP in the mice with GH, especially at higher doses (10 mg/kg/day and 15 mg/kg/day). However, oral gavage of melatonin at a dose of 10 mg/kg/day showed no obvious effect in altering the SBP of the WT mice (Fig. 1A), indicating the protective effect of melatonin in the mice with GH but not in the WT mice.

The urinary protein level is another important indicator for GH development, and accordingly, we detected the total urinary protein per day. As shown in Fig. 1B, the urinary protein level in the mice with GH was much higher than that in the control group of WT mice. Melatonin supplementation at different doses significantly attenuated urinary protein levels in the mice with GH. However, oral gavage of melatonin at a dose of 10 mg/kg/day had no effect on attenuating the urinary protein levels in the WT mice (Fig. 1B). These data indicated that maternal melatonin supplementation ameliorated hypertensive phenotypes in pregnant mice. As no difference was observed between the 10 and 15 mg/kg/day dose groups in the mice with GH, the 10 mg/kg/day dose was chosen for the next analysis. Calcium channel blockers are well-recognized drugs in the treatment of hypertension [26]. Therefore, amlodipine, a calcium channel blocker [27], was introduced to confirm the hypertensive symptoms. As expected, administration of amlodipine significantly reduced SBP and attenuated urinary protein levels in the mice with GH (Fig. 1C, D). These data further confirmed the successful establishment of the GH mouse model.

Maternal melatonin supplementation enhanced UtA endothelial-dependent relaxation

The effect of melatonin on the functions of UtAs was further detected. ACh-induced UtA endothelial-dependent relaxation in the mice with GH was significantly attenuated compared with that in the WT mice. In the WT mice, melatonin supplementation showed no influence on ACh-induced UtA endothelial-dependent relaxation. However, in the mice with GH, melatonin supplementation significantly enhanced ACh-induced UtA endothelial-dependent relaxation (Fig. 2).

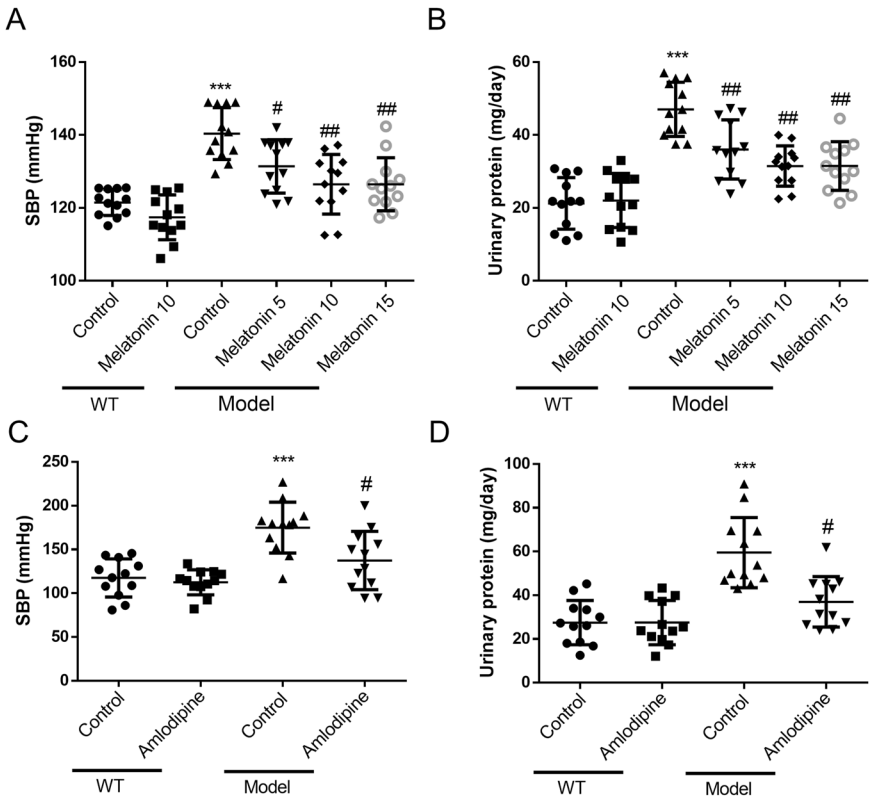

Fig. 1 Maternal melatonin supplementation ameliorated hypertensive phenotypes in the mice with GH. **A** Systolic blood pressure (SBP) was measured using tail-cuff plethysmography at GD17.5. Maternal melatonin supplementation significantly lowered SBP. Urinary protein levels expressed as mg/day (**B**) were measured at GD17.5 in pregnant mice of each group. Administration of amlodipine, a calcium channel blocker, significantly reduced SBP (**C**) and attenuated urinary protein levels (**D**) in the mice with GH. WT, wild type. Model, mice with GH. 12 mice for each group. Data are presented as the mean ± SD. $^{***}p < 0.001$, comparison between the control group of WT and model mice. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, comparison between the drug administration (melatonin or amlodipine) group and the control group of model mice

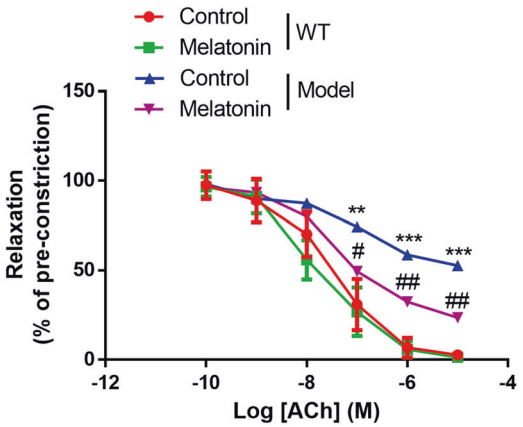

Fig. 2 Melatonin supplementation enhances UtA endothelial response to ACh. Maternal melatonin supplementation did not affect UtA endothelial responses to ACh in the WT mice but significantly enhanced relaxation in the GH model mice; 6 mice for each group. Data are presented as the mean ± SD. $^{**}p < 0.01$, $^{***}p < 0.001$, comparison between the control group of WT and model mice. $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, comparison between the melatonin and control group of model mice

The effect of melatonin supplementation on UtA hemodynamic parameters was also explored. GH development in the mouse model significantly decreased PSV (454.7 ± 124.7 in the WT control vs 357.7 ± 145.6 in the model control) and EDV (231.4 ± 82.1 in the WT control vs 187.4 ± 84.2 in the model control) and significantly increased RI (0.454 ± 0.05 in the WT control) vs 0.576 ± 0.13 in the model control) and PI (0.627 ± 0.06 in the WT control) vs 0.695 ± 0.15 in the model control). Melatonin supplementation showed no influence on PSV (454.7 ± 124.7 in the WT control vs 472.5 ± 131.9 in the WT melatonin), EDV (231.4 ± 82.1 in the WT control) vs 217.6 ± 79.7 in the WT melatonin), RI (0.454 ± 0.05 in the WT control vs 0.472 ± 0.07 in the WT melatonin), and PI (0.627 ± 0.06 in the WT control vs 0.631 ± 0.12 in the WT melatonin). In the GH model, melatonin supplementation significantly increased PSV (357.7 ± 145.6 in the model control vs 403.2 ± 151.3 in the model melatonin) and EDV (187.4 ± 84.2 in the model control vs 211.3 ± 87.3 in the model melatonin) and significantly decreased RI (0.576 ± 0.13 in the model control vs 0.523 ± 0.09 in the model melatonin) and PI (0.695 ± 0.15 in the model control vs 0.673 ± 0.11 in the model melatonin) (Table 1). These data suggested that maternal melatonin supplementation enhances UtA endothelial-dependent relaxation.

The BK_{Ca} potassium channel was involved in the effect of melatonin on UtA endothelial function

Given the crucial role of the potassium channel in the function of blood vessels, we detected which potassium channel was associated with melatonin-mediated UtA

Table 1 Effect of melatonin supplementation on uterine artery haemodynamic parameters

	WT		Model	
	Control	Melatonin	Control	Melatonin
PSV (mm s^{-1})	454.7 ± 124.7	472.5 ± 131.9	357.7 ± 145.6**	403.2 ± 151.3$^{\#}$
EDV (mm s^{-1})	231.4 ± 82.1	217.6 ± 79.7	187.4 ± 84.2*	211.3 ± 87.3$^{\#}$
RI	0.454 ± 0.05	0.472 ± 0.07	0.576 ± 0.13*	0.523 ± 0.09$^{\#}$
PI	0.627 ± 0.06	0.631 ± 0.12	0.695 ± 0.15*	0.673 ± 0.11$^{\#}$

Data are presented as mean ± SD.

PSV peak systolic velocity, *EDV* end-diastolic velocity, *RI* resistance index, *PI* pulsatility index.

*$p < 0.05$, **$p < 0.01$, comparison between control group of WT and Model mice. $^{\#}p < 0.05$, comparison between Melatonin and control group in Model mice.

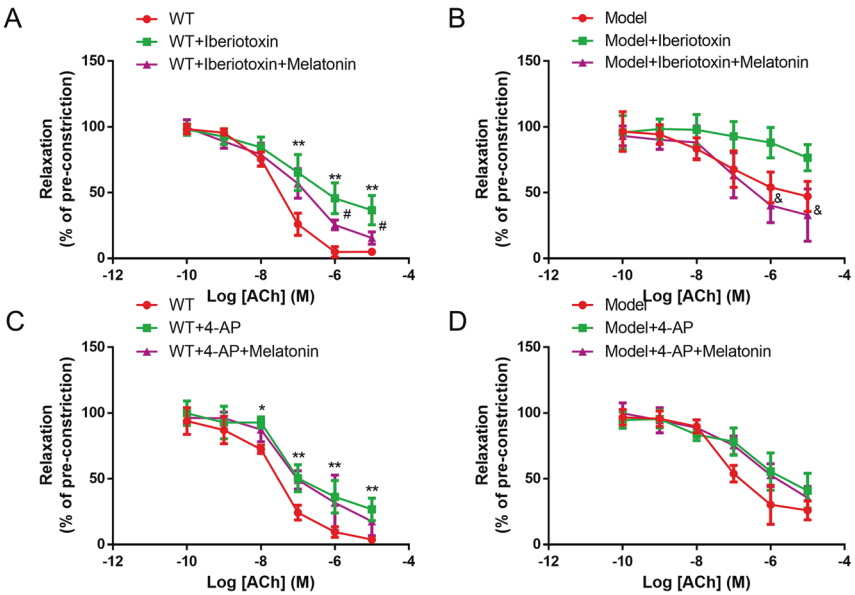

Fig. 3 Selective inhibition of the BK_{Ca} potassium channel attenuated the effect of melatonin. UtAs from the WT mice (**A**) or the GH model mice (**B**) were preincubated with 100 nM iberiotoxin, and endothelial response to ACh was tested. **$p < 0.01$, WT vs WT+iberiotoxin. $^{\#}p < 0.05$, WT+iberiotoxin vs WT+iberiotoxin+melatonin. UtAs from the WT mice (**C**) or the GH model mice (**D**) were preincubated with 1 mM 4-AP, and endothelial response to ACh was also tested. 10 mice for each group. Data are presented as the mean ± SD. **$p < 0.01$, WT vs WT+4-AP

vasorelaxation. In the WT mice, iberiotoxin (a selective inhibitor of BK_{Ca} channels) and 4-AP (a nonselective blocker of Kv channels) treatment significantly decreased ACh-induced UtA endothelial-dependent relaxation (Fig. 3A, C), indicating the crucial role of potassium channels in ACh-induced UtA endothelial-dependent relaxation. Melatonin supplementation dramatically enhanced UtA endothelial-dependent relaxation in the iberiotoxin-preincubated WT mice but not in the 4-AP-preincubated WT mice (Fig. 3A, C), indicating that the BK_{Ca} potassium channel, but not the Kv channel, was associated with melatonin-mediated UtA vasorelaxation.

Similarly, in the GH model mice, melatonin supplementation dramatically enhanced UtA endothelial-dependent relaxation in the iberiotoxin-preincubated WT mice but not in the 4-AP-preincubated GH mice (Fig. 3B, D), further indicating that the BK_{Ca} potassium channel, but not the Kv channel, was associated with melatonin-mediated UtA vasorelaxation.

Melatonin promoted BK_{Ca} potassium channel expression and function in UtAs

We further detected the expression levels of BK_{Ca} in UtAs. As shown in Fig. 4A, the BK_{Ca} expression level in the UtAs of the GH model mice was obviously decreased compared with that in the WT mice. In the WT mice, melatonin supplementation showed no influence on BK_{Ca} expression. However, in the GH model mice, melatonin supplementation dramatically enhanced BK_{Ca} expression in UtAs.

Western blot analysis of BK_{Ca} in UtAs revealed similar results: BK_{Ca} expression in UtAs of the GH model mice was much lower than that of the WT mice; melatonin supplementation showed no influence on BK_{Ca} expression in the WT mice, whereas significantly enhanced BK_{Ca} expression was observed in UtAs of the GH model mice (Fig. 4B, C). These data indicated that melatonin promoted BK_{Ca} potassium channel expression and function in UtAs.

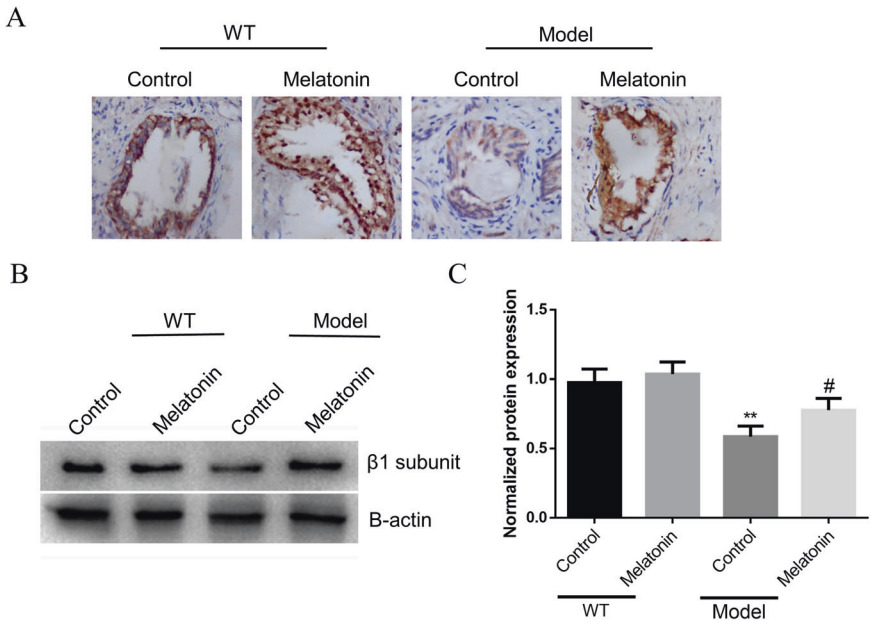

Fig. 4 Detection of BK_{Ca} expression in uterine arteries isolated from pregnant mice in each group as indicated. **A** Detection of BK_{Ca} β1 subunits on UtAs from different groups of mice by immunohistochemistry staining. Original magnification: 200×. **B**, **C** Western blot and quantitative analysis of BK_{Ca} β1 subunit expression on UtAs from different groups of mice; 10–12 mice for each group. $^{**}p < 0.01$, comparison between the control group of WT and model mice. $^{\#}p < 0.05$, comparison between melatonin and the control group of model mice

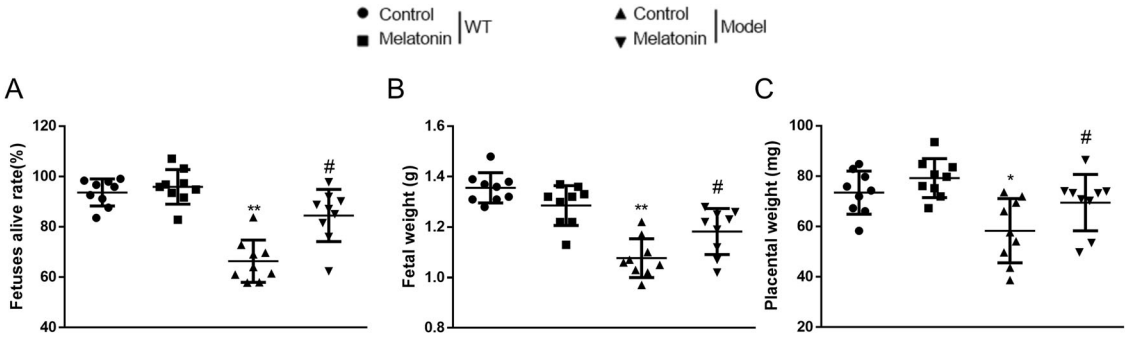

Fig. 5 Effects of melatonin on pregnancy outcomes in pregnant mice. The fetal live ratio (**A**), fetal weight (**B**), and placental weight (**C**) were evaluated on gestational day 18.5 9 mice for each group. Data are presented as the mean ± SD. $^{*}p < 0.05$, $^{**}p < 0.01$, comparison between the control group of WT and model mice. $^{\#}p < 0.05$, comparison between melatonin and control group of model mice

Effect of melatonin supplementation on pregnancy outcomes

We finally detected the effect of melatonin supplementation on pregnancy outcomes. The fetal live ratio, fetal weight and placental weight of the GH model mice were all significantly lower than those of the WT mice. Melatonin supplementation showed no influence on the fetal live ratio, fetal weight or placental weight of WT mice but significantly enhanced the fetal live ratio, fetal weight and placental weight of the GH model mice (Fig. 5A–C).

Discussion

Many pregnant women suffer from GH. However, the efficiency of treatments for GH in pregnant women is not satisfactory. In patients with high blood pressure, the first-morning melatonin level is negatively correlated with the hypertension incidence rate [28], and melatonin administration protects against age-related cardiovascular rhythms, including hypertension. Melatonin could also serve as a rational alternative in conservative treatment against resistant hypertension [29, 30]. Therefore, we explored the effect of melatonin using an established GH mouse model. We found that in the electrical stimulation-induced GH mouse model, melatonin supplementation at different doses (5 mg/kg/day, 10 mg/kg/day and 15 mg/kg/day) significantly suppressed SBP, urinary protein levels and total urinary protein levels per day. Maternal melatonin supplementation enhanced UtA endothelial-dependent relaxation, increased PSV EDV, and decreased RI and PI. Mechanistically, the BK_{Ca} potassium channel was involved in the effect of melatonin on UtA endothelial function, as preincubation with a selective BKCa channel inhibitor rescued UtA endothelial-dependent relaxation in the mice with GH. Melatonin promoted BK_{Ca} potassium channel

expression and function in UtAs. Our study indicated that melatonin ameliorates hypertension in hypertensive pregnant mice and suppresses hypertension-induced decreases in Ca^{2+}-activated K^+ channels in uterine arteries.

The potassium channel is crucial for the normal function of blood vessels for contraction [31, 32]. The expression level and function of potassium channels are closely associated with the physiological environment of cells; for example, high blood glucose and diabetes alter the functions of Kv channels [33, 34]. In the smooth muscle of the human umbilical vein, pregnancy-induced hypertension attenuates the expression level of Kv1.3 potassium channels [35]. BK_{Ca} is widely expressed in vascular smooth muscles and plays crucial roles in determining the transmembrane potential of vascular smooth muscles and eventually controlling vascular tone [36]. Inhibiting the BK_{Ca} channel or knocking out the expression of BK_{Ca}-related gene expression enhances blood pressure in pregnancy [37]. In pregnant sheep, pregnancy enhanced the channel activity of BK_{Ca} of uterine arteries, and more importantly, pregnancy attenuated the myogenic tone of uterine arteries [38]. Previous studies have indicated that the BK_{Ca} channel is associated with promoting blood circulation in the uterus and increasing blood flow to the uterus during pregnancy, which is very important, as the abundant energy supply for the fetus requires an increased blood flow supply of over 30% [37]. Accordingly, the physiological structure of blood vessels in the uterus has been adjusted to increase the vasodilator response and decrease the vasoconstrictor response. However, development of preeclampsia suppresses the expression level and function of BK_{Ca} [37]. Melatonin promotes vasodilation by directly or indirectly activating the BK_{Ca} channel [39, 40]. Our results demonstrated that in the GH mouse model, melatonin supplementation significantly enhanced the expression level of BK_{Ca} β1 subunits on UtAs. More importantly, the selective inhibitor of BK_{Ca} channels iberiotoxin rescued UtA endothelial-dependent relaxation, which was attenuated in the mice with GH compared with the WT mice. These data indicated that the protective role of melatonin in the mice with GH was at least partially dependent on BK_{Ca} channels.

It is important to note the limitations of this study. First, the effect of other potassium channels in GH was not investigated in this study, as a previous study reported that small conductance Ca^{2+}-activated K^+ channels were possibly associated with the protective role of melatonin in memory deficits in a rat model of cerebral hypoperfusion [41]. Second, the signaling pathways involved in melatonin-mediated BK_{Ca} potassium channels were not investigated in this study. Third, the interactions between melatonin and the BK_{Ca} potassium channel are complex. In another paper, melatonin improved memory deficits in a rat model of cerebral hypoperfusion by downregulating the expression level of BK_{Ca} potassium channels [41]. This finding may be attributed to the tissue-specific regulation of BK_{Ca} potassium channel activity by melatonin. The differential and even opposite roles of melatonin in different tissues may be caused by the different receptors of melatonin [40].

In summary, we found that melatonin supplementation ameliorated hypertensive phenotypes in the mice with GH, enhanced UtA endothelial function to ACh, and improved pregnancy outcomes in pregnant mice. Mechanistically, the BK_{Ca} potassium channel was involved in the effect of melatonin on UtA endothelial function, and melatonin promoted BK_{Ca} potassium channel expression and function in UtAs. Our study indicated that melatonin ameliorates hypertension in hypertensive pregnant mice and suppresses hypertension-induced decreases in Ca^{2+}-activated K^+ channels in uterine arteries.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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