Ventromedial Hypothalamus Activation Aggravates Hypertension Myocardial Remodeling Through the Sympathetic Nervous System

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Background: The ventromedial hypothalamus (VMH) is an important nuclei in receiving emotional stress, and emotional stress is a risk factor for cardiovascular diseases. However, the role of the VMH in cardiovascular diseases remains unknown. This study aimed to investigate the effects and underlying mechanisms of VMH activation on hypertension related cardiac remodeling in two-kidney-one-clip (2K1C) hypertension (HTN) rats.

Methods: Eighteen male Sprague-Dawley rats were injected with AAV-hSyn-hM3D(Gq) into the VMH at 0 weeks and then randomly divided into three groups: (1) sham group (sham 2K1C + saline i.p. injection); (2) HTN group (2K1C + saline i.p. injection); (3) HTN+VMH activation group (2K1C + clozapine-N-oxide i.p. injection). One week later, rats were subjected to a sham or 2K1C operation, and 2 weeks later rats were injected with clozapine-N-oxide or saline for 2 weeks.

Results: In the HTN+VMH activation group, FosB expression was significantly increased in VMH sections compared with those of the other two groups. Compared to the HTN group, the HTN+VMH activation group showed significant: (1) increases in systolic blood pressure (SBP); (2) exacerbation of cardiac remodeling; and (3) increases in serum norepinephrine levels and sympathetic indices of heart rate variability. Additionally, myocardial RNA-sequencing analysis showed that VMH activation might regulate the HIF-1 and PPAR signal pathway and fatty acid metabolism. qPCR results confirmed that the relative mRNA expression of HIF-1α was increased and the PPARα and CPT-1 mRNA expression were decreased in the HTN+VMH activation group compared to the HTN group.

Conclusions: VMH activation could increase SBP and aggravate cardiac remodeling possibly by sympathetic nerve activation and the HIF-1α/PPARα/CPT-1 signaling pathway might be the underlying mechanism.

Keywords: ventromedial hypothalamus, sympathetic nervous system, hypertension, cardiac remodeling, HIF-1α, PPARα, CPT-1
INTRODUCTION

The ventromedial hypothalamus (VMH) is an important emotion-related nuclei that responds to emotional stress and is involved in the regulation of emotional reactions. The VMH can be activated by emotional stress derived from environmental threats (1). Moreover, the activation of VMH nuclei by pharmacogenetics or optogenetic techniques could cause a variety of emotional reactions, such as anxiety, fear and anger (2–4). VMH activation plays an important role in emotional stress, which is a risk factor and prognostic factor for cardiovascular diseases (CVDs) (5). Clinical studies have found that patients who experience prolonged emotional stress were more likely to develop CVDs (6, 7). Moreover, emotional stress could increase the recurrence and death risk of adverse cardiovascular events (8, 9). However, the role of VMH nuclei in CVDs is currently unclear.

The VMH has been demonstrated to modulate the sympathetic nervous system activity in the periphery. Lesions in the VMH could reduce sympathetic outflow (10). In contrast, VMH activation by electronic stimulation or drug injection could increase the sympathetic nervous system activity (11, 12). It is well-known that excessive sympathetic nervous system (SNS) activation is involved in the onset and development of cardiovascular disease (13). Overactivated sympathetic nerves could induce increased blood pressure, cardiac remodeling and impaired cardiac systolic or diastolic function (13–17), while inhibition of sympathetic activity improves cardiac remodeling and cardiac function (18, 19). Therefore, we speculated that the SNS is the key to the link between VMH activation and CVDs.

In the present study, using hM3D(Gq) (excitatory) Designer Receptors Exclusively Activated Designer Drugs (DREADDs) to specifically activate the VMH, we aimed to investigate whether the activation of the VMH could exacerbate cardiac remodeling and increase systolic blood pressure in hypertension (HTN) rats via increased the sympathetic nervous system activity, and to investigate the potential molecular mechanisms.

METHOD

Animals

All experimental protocols were approved by the Animal Care and Use Committees of Renmin Hospital of Wuhan University. Male Sprague-Dawley rats (180–230 g) were housed at a constant temperature (25 ± 2°C) with 12 h light and dark cycles and fed standard rat food.

Abbreviations: VMH, Ventromedial hypothalamus; CVDs, Cardiovascular diseases; SNS, Sympathetic nervous system; DREADDs, Designer receptors exclusively activated designer drugs; HTN, Hypertension; 2K1C, Two-kidney, one-clip; CNO, Clozapine-N-oxide; 3V, The third ventricle; SBP, Systolic blood pressure; ANP, Atrial natriuretic peptide; BNP, Brain natriuretic peptide; HRV, Heart rate variability; HF, High frequency; LF, Low frequency; LF/HF, The ratio between LF and HF; NE, Norepinephrine; HIF-1α, Hypoxia-inducible factor-1α; PPARα, Peroxisome proliferator-activated receptors; CPT-1, Carnitine palmitoyl transferase 1; GO, Gene ontology; KEGG, Kyoto encyclopedia of genes and genomes.

Experimental Design

All rats received rAAV-hSyn-hM3D(Gq)-EGFP-WPRE-pA2/2 virus injection at 0 weeks, and then rats were randomly divided into following 3 groups (Figure 1A). (1) Sham group: One week after the virus injection, rats were subjected to a sham two-kidney one-clip (2K1C) operation. Two weeks after the sham operation, saline was given intraperitoneally (i.p.) for 2 weeks (2) HTN group: One week after the virus injection, rats were subjected to a 2K1C operation. Two weeks after the 2K1C operation, saline was injected (i.p.) for 2 weeks (3) HTN+VMH activation group: One week after the virus injection, rats were subjected to a 2K1C operation. Two weeks after the 2K1C operation, clozapine-N-oxide (CNO, 3.3 mg/kg, i.p.) was injected for 2 weeks. At 1 week, blood pressure was measured in all rats before the sham or 2K1C operation. Then, 2 weeks later, the blood pressure measurement was performed in all three groups. After saline or CNO injection for 2 weeks, the rats were subjected to blood pressure, ultrasonic cardiogram (UCG), and surface electrocardiogram (ECG) measurements before they were sacrificed. Then, blood samples, hearts and brain tissues were collected.

DREADDs Stereotaxic Injection

Rats were anesthetized with pentobarbital (2.5%) and placed in a stereotaxic instrument (RWD Life Science, Shenzhen, China). A midline skin incision was made on the head to expose the

![Image](314x140 to 541x394)

**FIGURE 1** | Experimental protocol and pharmacogenetics method. (A) Experimental protocol (n = 6 per group); (B) Schematic diagram and representative image showing virus injection and hM3D(Gq)-EGFP expression in the VMH at 3 weeks. The scale bar represents 100 μm. VMH, ventromedial hypothalamus; ECG, electrocardiogram; UCG, ultrasonic cardiogram; CNO, clozapine-N-oxide; 3V, the third ventricle.
surface of the skull. 100 nl of rAAV-hSyn-hM3D(Gq)-EGFP-WPRE-pA2/2 virus (Brain VTA, Wuhan, China) was injected into the bilateral VMH (20) (coordinates: anteroposterior −2.6 mm, mediolateral ±0.6 mm, dorsoventral −9.2 mm) at an infusion rate of 10 nL/min using a 10-µl Hamilton nanoinjector (Figure 1B). The injector was left in place for 10 min before withdrawal. Rats were allowed to recover for 1 w before the 2K1C operation.

Hypertension Model
Rats were anesthetized by i.p. injection of 2.5% pentobarbital. A silver clip (internal diameter 0.25 mm) was placed around the left renal artery. In the sham-operated group, animals underwent a similar surgical procedure without clip placement. After 2 weeks, blood pressure was measured. In the HTN and the HTN+VMH activation group, rats with systolic blood pressure (SBP) ≥150 mmHg were selected.

Measurement of Blood Pressure
At 1, 3, and 5 w after VMH injection, rats in each group were placed in a warm incubator at 40°C for 15 min. Then, the tail artery pressure of each rat was measured with a caudal artery cuff (BP-2010A, Softron Beijing Biotechnology Co., Ltd., Beijing, China) in a calm and quiet state. Blood pressure was continuously recorded three times to calculate the average.

Surface Electrocardiogram Recording
At 5 w, surface electrocardiogram (lead II) was then performed of each animal for 10 min (min) under anesthesia (2.5% pentobarbital sodium, i.p.). Heart rate variation (HRV) was analyzed from 5-min segments of ECG data with the HRV Module in LabChart software (ADInstruments, Castle Hill, NSW, Australia). The following power spectral variables were documented: the high frequency (HF, 0.75–2.5 Hz), the low frequency (LF, 0.20–0.75 Hz), and the LF/HF ratio.

Blood Sample Collection and Serum Noradrenaline Detection
After the completion of the ECG, 1 ml of arteria blood was collected and centrifuged at 3000 rpm for 15 min, then stored at −80°C. The norepinephrine (NE) concentration was measured with ELISA kit (CEA907Ge, Cloud-Clone, USA) following the instructions.

Histological and Immunofluorescence Analysis
The hearts and brains were rapidly removed, rinsed in ice cold 0.9% saline solution, blotted and fixed in phosphate-buffered 10% paraformaldehyde for histological study. Ventricles were isolated and cut into 2 fragments by a mid-ventricular coronal section. Each block was serially cut in the same direction into 4-µm thick sections. Hematoxylin and eosin stain (Servicebio, Wuhan, China) was used to determine myocytes cross area. Masson (Servicebio, Wuhan, China) stain was used for cardiac fibrosis analysis. TUNEL (Servicebio, Wuhan, China) was used to detect apoptosis of myocardial cells. Brains were cut into 5-µm sections for immunofluorescence analysis. The expression of Fos B (Abcam, USA) in VMH nuclei was used to evaluate neuronal activity. All analyses were quantified by Image Pro Plus (Media Cybernetics, Inc., Rockville, MD).

Cardiac Transcriptomics and Analysis
To determine the cardiac genes and pathways influenced by VMH activation, the cardiac transcriptome of rats in the HTN group and HTN+VMH activation group was assessed. Left ventricular tissues were collected after rats were sacrificed and stored at −80°C before use. Total RNA was extracted using TRIzol reagent and purified with the RNeasy Mini Kit according to the instructions to enrich mRNA. Then, mRNA was reverse transcribed into cDNA. The BGSQ-500 platform (BGI Inc., Wuhan, China) was used for gene sequencing to obtain raw reads. Clean reads were obtained from raw reads and then mapped to the rat reference genome (Rattus norvegicus, UCSC, rn6). The expression values were calculated as fragments per kilo base per million mapped reads (FPKM) (RSEM software, default, v1.2.8). R software was used for hierarchical clustering analysis, Gene Ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of differentially expressed genes (DEGs) between different groups. P-value < 0.05 was used as the threshold to select significant enrichment of the gene sets.

qRT-PCR
Total RNA was extracted from LV tissue using TRIzol reagent (Invitrogen™, Thermo) according to the manual. RNA concentration was measured using a NanoDrop2000 (Thermo). Then, cDNA was synthesized by using a RevertAid First Strand cDNA Synthesis Kit (Thermo). Quantitative real-time PCR was performed to quantify the relative mRNA expression of hypoxia-inducible factor-1α (HIF-1α, forward primer: 5′-ATGCCAGATCAGCACA-3′; reverse primer:5′-GGA CAAACTCCCTCACA-3′), peroxisomal proliferator-activated receptor α (PPARα, forward primer:5′-TGTGCTGAGTG AGAGA-3′; reverse primer:5′-CAGTGGAAGATCGGAC CT-3′), carnitine palmitoyl transferase 1 (CPT-1, forward primer:5′-TGACCAAAGCCTACC-3′; reverse primer: 5′-CAGGACCAAAGCACCAC-3′), atrial natriuretic peptide (ANP, forward primer: 5′-CGGTACCAGATACACAGCCA-3′; reverse primer: 5′-TCACACCCTCTCAGTGCAA-3′) and brain natriuretic peptide (BNP, forward primer: 5′-TTTCCT TAATCTGTGGCGCTGCT-3′; reverse primer: 5′-TGATCTG TAGATTGCTTGGTA-3′). Actin was used for normalization (forward primer:5′-CCGTGATGCTGCCTGCGT-3′; reverse primer: 5′-CTTGAATGCCGCATGCG-3′).

Statistics
SPSS 23.0 statistical software (SPSS Inc., Chicago, IL, USA) was applied for data analysis. The experimental results were expressed as the mean ± standard error of mean (SEM). Two-way ANOVA was used to analysis SBP. One-way ANOVA was used to analysis the rest of the data. Comparisons between any two means were performed by Tukey method. p < 0.05 represented that the difference was statistically significant.
Activation of VMH Nuclei Aggravated Cardiac Remodeling
The HE staining results revealed cardiomyocyte hypertrophy in the HTN and HTN+VMH activation group compared with the sham group. Additionally, the HTN+VMH activation group showed aggravated cardiomyocyte hypertrophy compared to HTN group, which was confirmed by quantification of individual cardiomyocyte cross-sectional areas (2858 ± 125 µm² vs. 5397 ± 501 µm² vs. 7893 ± 510 µm², sham vs. HTN vs. HTN+VMH activation, p < 0.01, Figure 3).

Cardiac fibrosis was assessed by Masson staining. Compared with the sham group, rats in the HTN group developed both perivascular and interstitial cardiac fibrosis (perivascular fibrotic area, 1.10 ± 0.12% vs. 3.95 ± 0.22%, sham vs. HTN, p < 0.01; interstitial fibrotic area, 3.39 ± 0.23% vs. 9.64 ± 1.04%, sham vs. HTN, p < 0.01). Additionally, compared with the HTN group, the HTN+VMH activation group showed further increases in cardiac fibrosis (perivascular fibrotic area, 3.95 ± 0.22% vs. 6.28 ± 0.47%, HTN vs. HTN+VMH activation, p < 0.05; interstitial fibrotic area, 9.64 ± 1.04% vs. 17.73 ± 1.46%, HTN vs. HTN+VMH activation, p < 0.01, Figure 3).

Myocyte apoptosis was assessed by TUNEL staining. The percentage of TUNEL positive cardiomyocytes per area of myocardium was statistically higher in the HTN+VMH activation group than in the HTN group (2.59 ± 0.51% vs. 0.84 ± 0.25%, HTN vs. HTN+VMH activation, p < 0.01, Figures 4A–C). To access the effect of VMH activation on hypertension-induced cardiac remodeling, we investigate the mRNA expression of ANP and BNP. The results suggested that in comparison with sham group, the relative mRNA expression of BNP was significantly increased in HTN group (p < 0.05). While, there were no significantly changes in ANP between the sham group and the HTN group (p > 0.05). Additionally, VMH activation could significantly increase the relative expression of ANP and BNP mRNA compared with HTN group (ANP, p < 0.01; BNP, p < 0.01, Figure 3C).

Activation of VMH Nuclei Increased Sympathetic Nervous System Activity
Heart rate variation and circulatory NE levels were used to evaluate the activity of the sympathetic nervous system. VMH activation significantly increased LF and the LF/HF ratio and markedly reduced HF compared with the HTN group (LF, 25.24 ± 1.98 nu vs. 42.06 ± 1.61 nu, HTN vs. HTN+VMH activation, p < 0.001; HF, 65.45 ± 1.79 nu vs. 49.99 ± 1.78 nu, HTN vs. HTN+VMH activation, p < 0.001, LF/HF, 0.44 ± 0.05% vs. 0.82 ± 0.05%, HTN vs. HTN+VMH activation, p < 0.001, Figures 4A–C). Similarly, the NE concentration in serum was significantly higher in the HTN+VMH activation group than the HTN group (511.03 ± 29.40 pg/mL vs. 667.82 ± 40.57 pg/mL, HTN vs. HTN+VMH activation, p < 0.05, Figure 4D).

Myocardial Transcriptomic Changes Resulting From VMH Activation
To investigate the effects of VMH activation on mRNA expression in the heart, RNA sequencing was used in the
HTN group and HTN+VMH activation group. Figure 5A demonstrated the differential gene expression heatmap between the HTN group and the HTN+VMH activation group (n = 3). The data showed that 41 genes were upregulated and 55 genes were downregulated (Figure 5B). KEGG pathway enrichment analysis and GO biological process analysis (the top five results with the highest P-value were selected) revealed significantly changes in PPAR signaling pathway, HIF-1 signaling pathway and fatty acid metabolism process (p < 0.05, Figures 5C,D). We further analyzed the related genes in these signaling pathways by qPCR and showed that VMH activation significantly increased the expression of HIF-1α mRNA, and
statistically decreased the expression of PPARα and CPT-1 mRNA ($p < 0.05$, Figure 5E).

**DISCUSSION**

**Major Findings**

The present study provided evidence that VMH activation could increase systolic blood pressure and hypertension-related cardiac remodeling by activating sympathetic nervous system. However, the HIF-1α/PPARα/CPT-1 signaling pathway might be the potential underlying mechanism (Figure 6).

**VMH Activation Regulated Cardiovascular Function and Aggravated Cardiac Remodeling via the Sympathetic Nervous System**

As one subnuclei of hypothalamus, VMH has been demonstrated to participate in emotional stress induced behavioral regulation (1, 21). The VMH has also been recognized to play an important role in modulating SNS outflow. Electrical stimulation or pharmacological (leptin, glucose, etc.) treatment of the VMH activated the sympathetic nervous system and increased serum norepinephrine levels (12, 22, 23). Rats with VMH lesions demonstrated downgraded sympathetic activity (10). As one of the vital connections between central brain nuclei and peripheral organs, the SNS could mediate the signal from the VMH to the cardiovascular system. Lim et al. (24) demonstrated that VMH activation engaged the sympathoexcitatory, leading to obesity-related hypertension. Additionally, Takenaka et al. (25) reported that baclofen (GABA receptor agonist) injected into the VMH decreased sympathetic nerve activity, BP and heart rate, and the reductions were significantly larger in spontaneously hypertensive rats than in Wistar-Kyoto rats. Furthermore, the depressor effects were abolished by intravenous pretreatment with phentolamine (adrenergic receptor blocker). The above findings indicate that VMH could modulate cardiovascular function via SNS activity.

In accordance with previous studies, the present study found that in comparison with the HTN group, the HTN+VMH activation group showed significantly increases in systolic blood pressure. Moreover, VMH activation could also statistically increase serum NE levels, LF and the LF/HF ratio, which have been used as markers of sympathetic activity.

**Activation of the SNS Might Aggravate Cardiac Remodeling via the HIF-1α/PPARα/CPT-1 Pathway**

To investigate the molecular pathways that caused the deterioration of myocardial remodeling after VMH activation, we used RNA-Seq to identify the changes in the transcriptome of the heart. Ultimately, we filtered out the PPAR signaling pathway, HIF-1 signaling pathway and fatty acid metabolism.

In the pathological process of cardiac remodeling, myocardial energy source converts fatty acids to glucose. HIF-1α has been considered involving in the conversion of pathological myocardial glucolipid metabolism and targeted PPARα to interfere with glucolipid metabolism (26). Studies have proven that myocyte hypertrophy could activate HIF-1α expression (27, 28), and the increase in HIF-1α expression in hypertrophic myocardium could cause a decrease in PPARα expression (29). While, PPARα could regulate the downstream effector CPT-1 to mediate the uptake and oxidation of myocardial fatty acid. Studies have reported that the reduction in PPARα expression would cause the downregulation of CPT-1 (30), and partial loss of CPT-1 would further aggravate LV systolic dysfunction and cardiac remodeling in pressure overload model mice (31). Moreover, it has been shown that the sympathetic nervous system might be involved in the regulation of the above signaling pathways. Studies demonstrated that isoprenaline and phenylephrine could increase HIF-1α expression (32, 33) and inhibit PPARα and CPT-1 expression (34, 35).

Consistent with previous research, in this research, we found that VMH activation could aggravate hypertension-relative cardiac remodeling. Additionally, in the present study, we observed the significant increase in HIF-1α mRNA relative expression and the decrease in PPARα and CPT-1 mRNA relative expression. The above results suggested that SNS overactivity due to VMH activation might affect the HIF-1α/PPARα/CPT-1 pathway, causing the deterioration of cardiac remodeling.

**Clinical Implication**

Evidence supports that the environmental threats causing emotional stress could activate VMH firing (1, 21). Additionally, VMH activation through optogenetics or pharmacogenetics methods could increase anxiety, fear, defensive or aggressive emotional reactions, and VMH inhibition could decrease above emotional reactions (2–4). The above results indicate that the VMH plays the key role in responding to emotional stress. Emotional stresses such as anxiety, fear and anger were the
FIGURE 5 | The RNA-seq and qPCR analysis results. (A) Heatmap of expression genes between HTN and HTN+VMH activation group (n = 3 per group); (B) Number of up-regulated and down-regulated genes between HTN and HTN+VMH activation group (n = 3 per group); (C) KEGG pathway enrichment analysis between HTN and HTN+VMH activation group; (D) GO biological process analysis between HTN and HTN+VMH activation group; (E) The relative mRNA expression of HIF-1α, PPARα, and CPT-1 in sham group, HTN group, and HTN+VMH activation group. Values are presented as mean ± SEM (n = 4 per group). **p < 0.01; vs. sham group; ##p < 0.01 vs. HTN group.

independent risk factors and predictors of hypertension (36). Clinical studies have shown that people under emotional stress would more likely to suffer from hypertension (37, 38). Furthermore, prolonged exposure to emotional stressors would cause poor prognosis of hypertension. Compared with other hypertensive patients, hypertensive patients with higher
emotional stress showed blood pressure elevation (39), poor blood pressure control (40), sympathetic nervous system overactivation and cardiac remodeling deterioration (41, 42).

Therefore, evaluating the activity of the VMH through fMRI or PET-CT might help to predict hypertensive patient prognosis. On the other hand, the present study results suggest that pharmacological inhibition of HIF-1α might improve the outcomes of hypertensive patients with emotional stress. This study might provide a novel target for preventing ventricular remodeling in hypertensive patients with emotional stress.

Limitations
There are several limitations of this research. First, we activated all neurons in the VMH. Whereas, there are multiple kinds of neurons in the VMH. Further research needs to identify the specific role of each kind of neuron in cardiovascular disease. Second, VMH neurons show sexual dimorphisms and could regulate sex-dependent emotional reactions (43, 44). In this study, we demonstrated the effects of VMH activation in male rats, therefore, further study should focus on the cardiovascular effect of VMH activation in the female subjects. Third, we only investigate the effects of VMH activation on early-stage cardiac structure remodeling. In the future research, we will take a longer observation for the cardiac structure and function changes.

CONCLUSION
In conclusion, activation of VMH could enhance SBP and aggravate hypertensive relative cardiac remodeling via sympathetic nerve activation, and the underlying mechanism might be the HIF-1α/PPARα/CPT-1 pathway.

DATA AVAILABILITY STATEMENT
The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: SRA, PRJNA748709.
ETHICS STATEMENT

The animal study was reviewed and approved by Animal Care and Use Committees of Renmin Hospital of Wuhan University.

AUTHOR CONTRIBUTIONS

HJ and XZ designed the study. YZ, ZHL, and ZIL analyzed data and wrote and revised the manuscript. HZ, XX, ZeL, and HC performed the animal experiments and statistical analysis. YW, ZZ, MW, YL, and LZ edited manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2021.737135/full#supplementary-material
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