

SHORT COMMUNICATION

Npy2r-expressing postganglionic sympathetic neurons modulate cardiac functions

Sachin Sharma^{1,2*} 

¹UCLA Neurocardiology Centre for Excellence, UCLA Health, Los Angeles, CA 90095, United States of America

²Graphic Era University, Dehradun, India

Abstract

Background: Cardiac disorders are either inherited or acquired, reflecting deformities in their structural or functional characteristics. Despite significant advances in cardiovascular drugs and surgical procedures, no breakthroughs have been achieved. The cervicothoracic ganglia, also known as stellate ganglia, located within the paravertebral chain, are known to innervate myocardial tissues in a heterogeneous manner; however, their therapeutic potential for managing myocardial diseases is not yet fully understood. **Methods:** Our single-cell sequencing transcriptomic data from wild-type stellate ganglia demonstrated that cardiac-innervating *Npy2r*-expressing neuronal subpopulations consistently innervate the myocardium. To investigate whether these neuronal subpopulations influence cardiac functions, we used the *Npy2r*-IRES-Cre crossed with the Ai32-(ChR2(H134R)/EYFP) strain. The offspring with genotypes *Npy2r⁺::ChR2⁺*, 6 to 8 weeks old littermates, were selected for optical stimulation via an optical fibre connected to the OptoEngine (473 nm, 400 mW, OptoEngine). **Results:** We observed a significant increase in heart rate among *Npy2r⁺::Ai32⁺* heterozygous mice compared to control Ai32⁺ mice following optical stimulation at various frequencies: 1Hz, 5Hz, 10Hz, 15Hz, and 20Hz. Stellate ganglia isolated from *Npy2r⁺::Ai9⁺* heterozygote mice showed positive neuronal staining for tdTomato expression. **Conclusion:** These findings clearly indicate that *Npy2r*-expressing neuronal subpopulations in the cervicothoracic ganglia influence heart rates during in vivo optical stimulation of stellate ganglia. **Relevance for Patients:** The study provides novel targets for devising anti-adrenergic therapies against refractory ventricular arrhythmia. These novel targets should be used as the combinatorial therapies along with β -blockers and surgical interventions.

***Corresponding author:**
Sachin Sharma
(sachinhcu07@gmail.com)

Citation: Sharma S. *Npy2r*-expressing postganglionic sympathetic neurons modulate cardiac functions. *J Clin Transl Res.* 2026;12(4):026150025. doi: 10.36922/JCTR026150025

Received: April 11, 2026

Revised: May 21, 2026

Accepted: May 25, 2026

Published online: June 12, 2026

Copyright: © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons AttributionNonCommercial 4.0 International (CC BY-NC 4.0), which permits all non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Publisher's Note: AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Keywords: Postganglionic sympathetic neurons; Optogenetic stimulation; Channelrhodopsin-2; Neuropeptide-Y; Neuropeptide-Y2r receptors

1. Introduction

Cardiac disorders such as myocardial infarction, arrhythmogenic cardiomyopathy, and atrial fibrillation remain one of the leading causes of mortality across the global population.¹ The structural and functional deformities related to cardiovascular diseases can be either inherited or acquired over the course of a lifetime.² At present, various therapeutic aspects in the form of cell and gene therapies, neuromodulation,

and neuroscience-based therapeutics have been employed for cardiac disorder treatment.^{2–4} However, many of these have failed in clinical trials or have been unsuccessful due to their high toxicity and limited efficacy. The cardiac autonomic nervous system comprises sympathetic and parasympathetic nervous systems, which regulate cardiovascular functions precisely in health and disease. During cardiac dysfunction, increased sympathetic tone and withdrawal of the parasympathetic tone become obvious during myocardial disorders.^{4,5}

The sympathetic tone of myocardial tissues is mediated by stellate and T2 ganglia that reside within the cervicothoracic region. The bilateral sympathectomy (removal of left and right stellate ganglia) has already been under investigation for the treatment of refractory ventricular arrhythmia.^{6,7} Although the procedure is effective, the arrhythmia persists. The remodeling of stellate ganglia during myocardial infarction comprises increased neuronal size and adrenergic tone, specifying higher immunoreactivity for tyrosine hydroxylase (TH) and neuropeptide-Y (NPY).⁸ Neuropeptide-Y is a pro-arrhythmic neurotransmitter, and it has been under investigation for decades.⁹ Circulating plasma level of NPY is also elevated in heart failure patients, as measured in ELISA assays, isolated samples from the coronary sinus vein.^{10,11} Therefore, elucidating the mechanistic role of NPY is crucial in identifying its therapeutic use for myocardial diseases.

Previously, we identified three major adrenergic neuronal subpopulations, NA1a, NA1b, and NA3 subtypes that innervate myocardial tissues and the NA1b subpopulation is increased in heart-failure settings.^{12–14} Since NPY's effects are exerted and amplified via its receptors, NPY-Y1, NPY-Y2, and NPY-Y5 receptors.¹⁵ In the current study, we employed an optogenetic method to dissect the role of a specific postganglionic sympathetic neuronal subpopulation (*Npy2r*) in modulating the cardiac functions, specifically in heart rate variability.¹⁶

2. Methods

2.1. Animals

Mice strains *Npy2r*-IRES-Cre, Ai32-(ChR2(H134R)/EYFP), and B6.Cg-Gt(ROSA)26Sortm9(CAG-tdTomato)Hze/J were purchased from Jackson Laboratories. The study (protocol number: 18-048) was approved by the UCLA Institutional Animal Care and Use Committee. Adult male mice, aged between 6 and 8 weeks, were housed under standard laboratory conditions (12-hour light/dark cycle) with *ad libitum* access to food and water.

2.2. In vivo cervicothoracic ganglia stimulation

Heterozygous mice *Npy2r*^{+/-}::Ai32^{+/-} were chosen for

optical stimulation at the right stellate ganglia (RSG). Mice were anaesthetized with isoflurane (Induction at 4%, maintenance at 2%, inhalation) (Isoflurane Vaporiser, SOMNI Scientific). Two needle electrodes were inserted subcutaneously into the right forearm and the left hind leg to obtain lead II electrocardiograms (Grass RPS 107 Regulated Power Supply, Grass Instrument Co.; Grass P511 AC Amplifier, Natus Neurology). With the use of a dissecting microscope (SZ-CTV Olympus Dissecting Microscope; KL 2500 LED Illuminator, Schott), a midline neck incision was performed to intubate and mechanically ventilate mice at 150 bpm (SAR-830/P Ventilator, CWE, Inc). A left thoracotomy was performed at the second intercostal space to expose the RSG located along the sympathetic trunk near the first rib. A laser-coupled optical fiber (473 nm, 400 mW, Optic Engine) was positioned for focal illumination above the craniomedial RSG. The stimulation frequency (at 10 ms and 126 mW) and pulse width (at 10 Hz and 126 mW) were used to measure the heart rate for control and *Npy2r*^{+/-}::Ai32^{+/-} mice. We illuminated the optical fiber at 473 nm while positioned at the RSG and stimulated at different frequencies: 1 Hz, 5 Hz, 10 Hz, 15 Hz, and 20 Hz. All stimulations were performed for 10 s with 5 min between stimulations for the heart rate to return to baseline values. We recorded an electrocardiogram (ECG) during these stimulation frequencies using a differential amplifier (A-M Systems, Model 1700 and Grass, P511) and recorded via PowerLab 8/35.

2.3. Stellate ganglia isolation and whole-mount tissue fixation

The protocol to isolate stellate ganglia tissues from mice was adapted from a previously published article¹². Briefly, mice were anaesthetized with 3% isoflurane for 5 min until no reflexes were observed and perfused with 50 ml ice-cold 0.01 M phosphate buffer saline (PBS; consisting of 10 mM potassium phosphate at pH 7.4 and 150 mM NaCl) containing heparin, followed by 50 mL freshly prepared, ice-cold 4% paraformaldehyde in PBS. Afterwards, stellate ganglionic tissues were isolated using a dissecting microscope, and tissues were fixed in 4% paraformaldehyde overnight at 4 °C, washed, and stored in 0.01 M PBS at 4 °C. Stellate ganglia were collected bilaterally (both right and left sides) from all animals and mounted on the slide-chamber under a light-protecting sheet for whole tissue imaging.

2.4. Confocal microscopy and image processing

High-fluorescent images were acquired on a confocal laser scanning microscope, LSM 880 Upright (Carl-Zeiss, Germany). The laser lines used were 405 nm (diode [405-

30]) for excitation of DAPI, 488 nm (argon) for Alexa-488, 561 nm (DPSS [561-10]) for Cy3, and 633 nm (HeNe) for Alexa-647. Fluorescence and bright-field illumination modes were used during the image acquisition process. Samples were visualized through plan apochromat 10×/0.45 air, plan apochromat 20×/0.8 air, and plan apochromat 63×/1.4 oil objectives.

2.5. Statistical analysis

GraphPad Prism 9.0.1 was used for data handling, analysis, and graph generation. For statistical significance, we performed a two-way analysis of variance (ANOVA) test to analyze the data, along with a Bonferroni correction, to test the null hypothesis. All data are shown here as individual data points. *P*-values are expressed as * (*p* < 0.05), ** (*p* < 0.01), *** (*p* < 0.001), and **** (*p* < 0.0001) in the figures.

3. Results

In the current study, we examined the role of specific *Npy2r*-expressing neuronal subpopulations within the stellate ganglia. Postganglionic sympathetic neurons in the stellate ganglia comprise eight subpopulations, including five adrenergic (NA1a, NA1b, NA1c, NA2, and NA3), two cholinergic (ACh1 and ACh2), and one glutamatergic subtype (Glut1). Our previous scRNAseq analysis demonstrated that the receptor *Npy2r* is expressed in the NA1b subtype. However, its functional role in cardiac sympathetic modulation remains unclear. Therefore, to test our hypothesis that *Npy2r*-expressing subpopulations within the stellate ganglia may influence cardiac functions, we employed an optogenetic stimulation method (Figure 1).

We crossed *Npy2rCre* mice with Ai32 (Ch2R-expressing mice) and stimulated heterozygous *Npy2r^{+/+}::Ai32^{+/-}* offspring at gradually increasing stimulation frequencies: 1Hz, 5Hz, 10Hz, 15Hz, and 20Hz. Figure 2A shows the baseline heart rate for *Npy2rCre^{+/+}::Ai32^{+/-}* and control mice. Figure 2B depicts heart rate during pre-stimulation and post-stimulation in *Npy2rCre^{+/+}::Ai32^{+/-}* mice. Figure 2C and 2D illustrate changes in heart rate at different stimulation frequencies for both genotypes, presented as a bar-chart plot and a trend-line graph. We observed maximal heart rate changes at 5 Hz, 10 Hz and 20 Hz for *Npy2rCre^{+/+}::Ai32^{+/-}* versus Ai32^{+/-} mice (Figure 2C and 2D) representing the maximal cardiac sympatho-excitation.

To validate further, expression of *Npy2r* neurons in stellate ganglia, we visualized tissues under the microscope for tdTomato expression in stellate ganglia isolated from *Npy2rCre^{+/+}::Ai9^{+/+}* mice and confirmed the staining pattern (Figure 3). We observed individual neurons stained positive for tdTomato expression in stellate ganglia

tissues that represent *Npy2r*-expressing neurons (Figure 3). These results were confirmatory that stimulating specific sympathetic neuronal subpopulations modulates cardiac functions, providing new avenues for therapeutic applications for cardiovascular-related disorders.

4. Discussion

Cardiovascular-related disorders remain one of the major reasons for morbidity and mortality across the globe.^{17,18} Several therapeutic applications, such as renin-angiotensin-aldosterone (RAAS) blockers, Ca²⁺ channel blockers, and β-blockers, have been employed for treatment purposes; however, the success rate is very limited and has severe side effects.^{19,20} Alternatively, neuroscience-based therapeutics for cardiovascular diseases have been introduced over the past few decades.^{21,22} The neural innervation of cardiac tissues is a fact that is regulated at three layers of the nervous system: the central nervous system, the extracardiac intrathoracic nervous system, and the intrinsic cardiac nervous system.^{23–27} Our work is focused mainly on the extracardiac intra-thoracic innervation of myocardial tissues. Previously, several studies reported that the stellate ganglia located in the intrathoracic cavity interplays cardiac regulation at structural and functional contexts, suggesting a vital role in neuroscience-based cardiovascular therapeutics.^{5,13,28,29} We also defined neuronal subpopulations residing in the stellate ganglia that innervate myocardial tissues using scRNAseq analysis and retrograde viral tracing methods.^{12,14} We identified high-NPY and low-NPY expressing cells that innervate myocardial tissues. The neurotransmitters released from cardiac innervating axons modulate cardiac functions. Examples include epinephrine, norepinephrine, neuropeptide Y, and galanin, released from the sympathetic nervous system and acetylcholine, released from the vagus nerve.^{9,30–33}

In addition to the effect of norepinephrine, several other lines of evidence suggest that NPY released during sympathetic activation may lead to the progression of ventricular arrhythmia via NPY receptors present on rat and human cardiomyocytes.^{34,35} Sympathetic neurons residing in stellate ganglia are heterogeneous subpopulations and innervate the myocardial tissues viscerally.^{13,36} Our study had previously revealed that three major adrenergic neuronal subpopulations (NA1a, NA1b, and NA3) participate in myocardial innervation.¹² However, the influence of these neuronal subpopulations on cardiac function remains unknown. To resolve the functions of these neuronal cell types, we crossed *Npy2rCre* mice with Ai32 mice, and offspring carrying the heterozygous genotype were chosen for optical stimulation. In a previous study, it has already

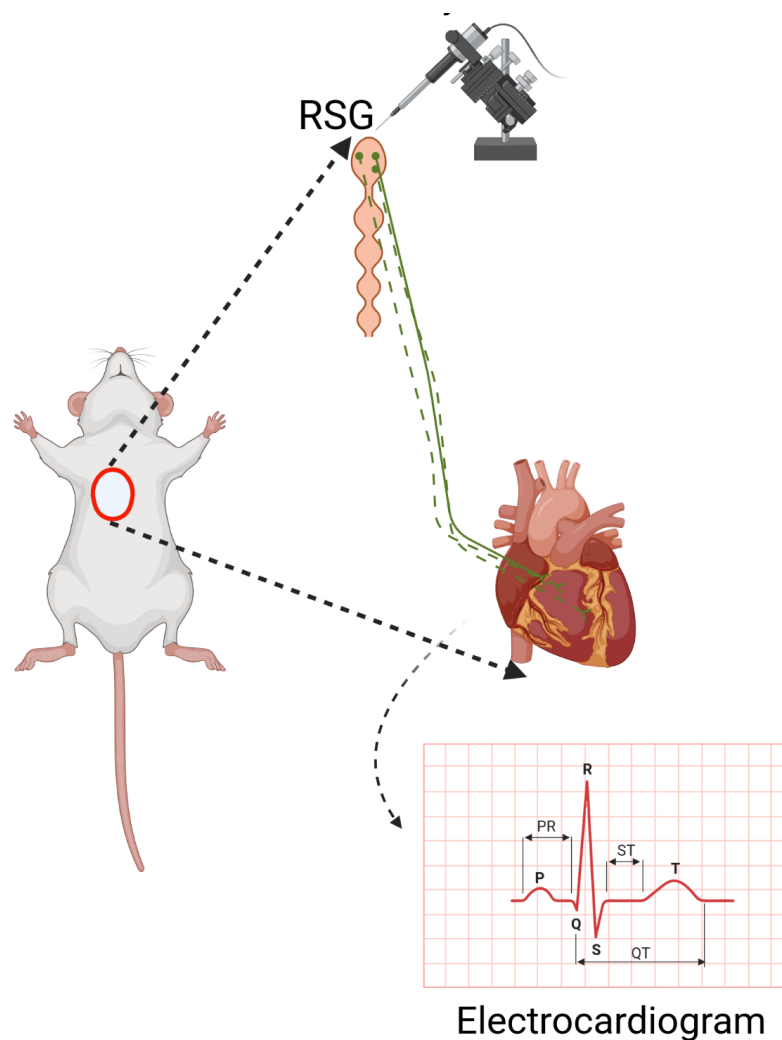


Figure 1. A representative image of optogenetic stimulations of cardiac neurons in the stellate ganglia and ECG parameters measurement

been shown that channelrhodopsin-2 (ChR2) expressing cells permit the entry of Na^+ , K^+ , and Ca^{2+} ions, allowing the cells to depolarize.³⁷ This depolarization leads to initiating the action potentials across postganglionic neurons and the release of neurotransmitters within the postsynaptic clefts.¹³

In the current study, we created animals that carried *Npy2r*-expressing cells, along with Ch2R expressions. Our results clearly indicate that blue-light-mediated induction of these neuronal cell types affects cardiac function, as measured by ECG response. NPY is a pro-arrhythmic agent and exerts effects via NPY receptors (Y1, Y2, and Y5) on myocardial tissues.^{9,34,35,38} However, the current study potentially evaluates the specific role of *Npy2r*-expressing neuronal subpopulations within stellate ganglia and how they modulate cardiovascular functions. In the

current work, we chose to stimulate only the RSG, not the left stellate ganglia, to evaluate the heart rate change. Since the RSG innervates the sinoatrial (SA) node and anterior ventricles, whereas the left stellate ganglion primarily innervates the posterior aspect of the ventricles, only RSG stimulation was expected to directly influence SA node activity and heart rate.^{29,39–41} Therefore, *Npy2r*-expressing neuronal subpopulations in RSG pre- and post-stimulation have provided clear evidence of heart rate changes measured simultaneously.

The current work opens new avenues for neuroscience-based cardiovascular therapeutics. A previous study has shown the localization of NPY-Y2 receptors on autonomic ganglia.⁴² It has also been shown that NPY-Y2R receptors are involved in fine-tuning the norepinephrine secretions in the periphery and myocardial tissues and mediate

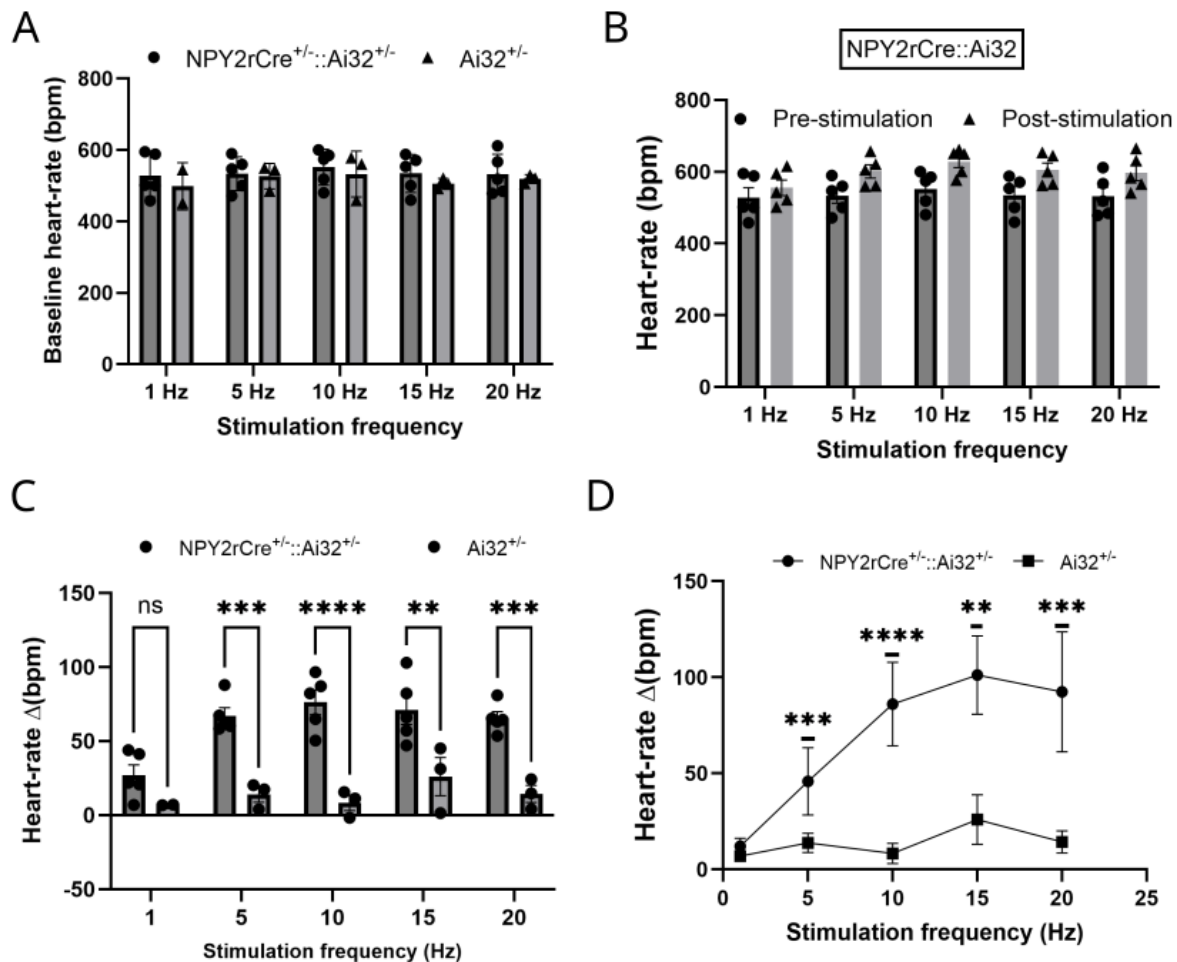


Figure 2. Postganglionic sympathetic neurons expressing *Npy2r* present within the stellate ganglion modulate cardiac functions. We stimulated *Npy2r* neurons optically at 473 nm using optical fibers attached to the OptoEngine. (A) The baseline heart rate calculated for *Npy2rCre::Ai32* mice versus only *Ai32* mice. (B) Heart rate for *Npy2rCre* mice at various frequencies during pre-stimulation and post-stimulation. (C) A bar-plot graph representing heart rate differences for *Npy2rCre::Ai32* versus *Ai32* mice during stimulations at various frequencies: 1 Hz, 5 Hz, 10 Hz, 15 Hz, and 20 Hz. (D) The continuous dot-plot graph analyses the change in heart rates for *Npy2rCre::Ai32* mice versus *Ai32* at various stimulation frequencies. ($n=5$ mice for *Npy2rCre* and $n=3$ mice for *Ai32*).

sympatho-vagal crosstalk neurotransmission.^{15,43} The blockade of presynaptic Y2R receptors results in the reduction of acetylcholine release and promotes vagal effects while reducing cardiac sympatho-excitation.⁴³ However, these studies have formed the basis of the inhibitory effects on cardiac sympatho-excitation, while NPY-Y2R receptors are localized on myocardial tissues or the surrounding vasculature tissues and mediate the effects of circulating NPY neurotransmitters.¹⁵ Our work provides a novel discovery about the presence of NPY-Y2R-specific neuronal subpopulations in stellate ganglia, along with already known NPY-expressing neurons in stellate ganglia.¹² The additional experimental validations of NPY-Y2R mediated mechanistic roles in cardiac

sympatho-excitation during health and disease have major issues in finding an adequate number of cells, since the size of the tissue is very small in the mouse species.¹² Moreover, in heart failure conditions, these numbers become even lower, complicating the findings to reach a significant conclusion for the transcriptomic and functional studies.¹⁴

Several limitations of this study should be acknowledged. First, the current study involved only a limited number of adult male mice. Second, we only conducted experiments to show acute functional effects. Future studies will involve the use of *Npy2r*-innervated cardiac remodeling studies.

5. Conclusion

The current study concludes that sympathetic neuronal

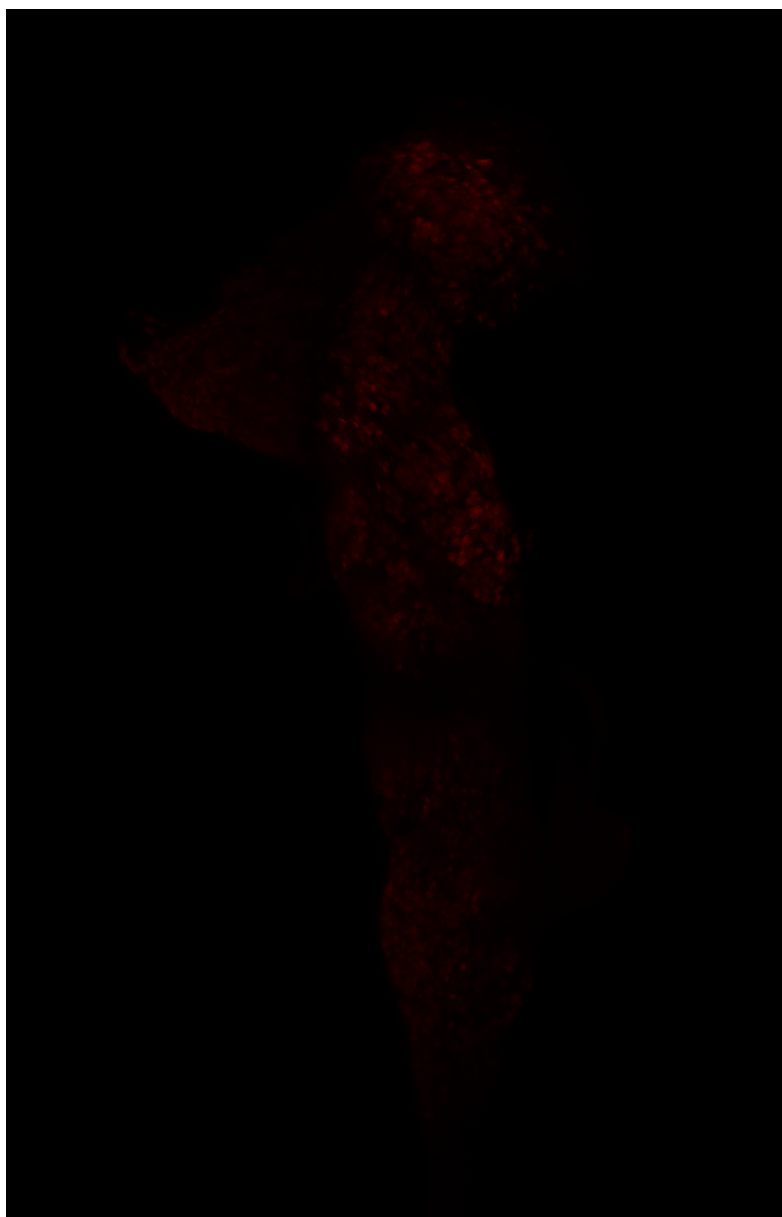


Figure 3. A confocal microscope image of the right stellate ganglia tissue isolated from *Npy2rCre* mice crossed with the Ai9 strain. The image shows expression of tdTomato in *Npy2r*-expressing neurons in stellate ganglia from *Npy2rCre*^{+/+};*Ai9*^{+/-} mice strains. The study further validates that postganglionic neurons in the stellate ganglia express *Npy2r* receptors and modulate cardiac function.

subpopulations that express *Npy2r* in the stellate ganglia modulate cardiac function, especially heart rate change during baseline and stimulation periods. However, the study still requires further validation to determine how these neuronal subpopulations communicate with myocardial tissues in heart failure scenarios.

Acknowledgments

The authors would like to thank Graphic Era Deemed to

be University for providing the necessary assistance during the preparation of the manuscript.

Funding

The current research has been partially funded from American Heart Association as a postdoctoral award fellowship to Sachin Sharma during his work at the UCLA Cardiac Arrhythmia Centre.

Conflict of interest

The authors declare they have no competing interests.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

The work does not involve the use of any human subjects for study. The consent to use mouse strains was approved by the UCLA Institutional Animal Care and Use Committee under the protocol (Protocol number: 18-048).

Consent for publication

Not applicable.

Availability of data

Data are available from the corresponding author upon request.

References

- Joseph P, Lanos F, Roth G, *et al.* Cardiovascular disease in the Americas: the epidemiology of cardiovascular disease and its risk factors. *Lancet Reg Health – Am.* 2025;42:100960. doi: 10.1016/J.LANA.2024.100960
- Kumar V, Kalishwaralal K, Chauhan C, Singh G, Barnwal RP, Sharma S. AAV viral vectors as therapeutic interventions for inherited or non-inherited cardiac disorders: current aspects and future prospects. *Front Med.* 2025;12:1678325. doi: 10.3389/FMED.2025.1678325
- Shivkumar K, Ajjola OA, Anand I, *et al.* Clinical neurocardiology defining the value of neuroscience-based cardiovascular therapeutics. *J Physiol.* 2016;594(14):3911-3954. doi: 10.1113/JP271870
- Ajjola OA, Aksu T, Arora R, *et al.* Clinical neurocardiology: defining the value of neuroscience-based cardiovascular therapeutics - 2024 update. *J Physiol.* 2025;603(7):1781-1839. doi: 10.1113/JP284741
- Hanna P, Hoover DB, Kirkland LG, *et al.* Noradrenergic and cholinergic innervation of the normal human heart and changes associated with cardiomyopathy. *Anat Rec.* 2025;309(2):417-450. doi: 10.1002/ar.25686
- Sujith MA, Varsha Rakshitha P, Prakash VS. Bilateral stellate ganglion block calms electrical storm. *IHJ Cardiovasc Rep.* 2024;8(3):87-89. doi: 10.1016/J.IHJCVR.2024.09.002
- Skinner C, Ayoub M, Geara E, *et al.* Alternative Approaches to Bilateral Stellate Ganglion Block for Treatment of Refractory Ventricular Arrhythmia. *Case Rep Anesthesiol.* 2025;2025(1):2691681. doi: 10.1155/CRIA/2691681
- Ajjola OA, Yagishita D, Reddy NK, *et al.* Remodeling of stellate ganglion neurons after spatially targeted myocardial infarction: Neuropeptide and morphologic changes. *Heart Rhythm.* 2015;12(5):1027-1035. doi: 10.1016/j.hrthm.2015.01.045
- Bloxson R, Liu K, Handford C, *et al.* The cardiac sympathetic co-transmitter neuropeptide-Y is pro-arrhythmic in human cardiomyocytes by lengthening activation-recovery interval. *Eur Heart J.* 2024;45(Supplement_1):ehae666.3774. doi: 10.1093/eurheartj/ehae666.3774
- Zaglia T, Ajjola OA. The Reappraisal of Neuropeptide Y as Biomarker and Therapeutic Target in Arrhythmic Disorders. *Clin Electrophysiol.* 2025;11(4):664-666. doi: 10.1016/J.JACEP.2025.01.012
- Ajjola OA, Chatterjee NA, Gonzales MJ, *et al.* Coronary Sinus Neuropeptide Y Levels and Adverse Outcomes in Patients With Stable Chronic Heart Failure. *JAMA Cardiol.* 2020;5(3):318-325. doi: 10.1001/JAMACARDIO.2019.4717
- Sharma S, Littman R, Tompkins JD, *et al.* Tiered sympathetic control of cardiac function revealed by viral tracing and single cell transcriptome profiling. *eLife.* 2023;12. doi: 10.7554/eLife.86295
- Rajendran PS, Challis RC, Fowlkes CC, *et al.* Identification of peripheral neural circuits that regulate heart rate using optogenetic and viral vector strategies. *Nat Commun.* 2019;10(1). doi: 10.1038/s41467-019-09770-1
- Sharma S. Dilated cardiomyopathy remodels cardiac neuronal subtypes in a murine model. *bioRxiv.* Preprint posted online August 7, 2025. doi: 10.1101/2025.08.05.668697
- Tan CMJ, Green P, Tapoulal N, Lewandowski AJ, Leeson P, Herring N. The Role of Neuropeptide Y in Cardiovascular Health and Disease. *Front Physiol.* 2018;9:1281. doi: 10.3389/FPHYS.2018.01281
- Berling D, Baroni L, Chaffiol A, Gauvain G, Picaud S, Antolík J. Optogenetic Stimulation Recruits Cortical Neurons in a Morphology-Dependent Manner. *J Neurosci.* 2024;44(49):e1215242024. doi: 10.1523/JNEUROSCI.1215-24.2024
- Samuel M, Elsookari I, Sapp JL. Ventricular Tachycardia Burden and Mortality: Association or Causality? *Can J*

- Cardiol.* 2022;38(4):454-464.
doi: 10.1016/J.CJCA.2022.01.016
18. Azeem B, Khurram L, Sharaf B, *et al.* Unmasking Arrhythmia Mortality: A 25-Year Analysis of Trends and Disparities in the United States (1999–2023). *Clin Cardiol.* 2025;48(3):e70109.
doi: 10.1002/CLC.70109
19. Tripathi R, Sullivan R, Fan THM, *et al.* Enhanced heart failure, mortality and renin activation in female mice with experimental dilated cardiomyopathy. *PLoS ONE.* 2017;12(12):e0189315.
doi: 10.1371/journal.pone.0189315
20. Lisi F, Parisi G, Gioia MI, *et al.* Mineralcorticoid Receptor Antagonist Withdrawal for Hyperkalemia and Mortality in Patients with Heart Failure. *Cardiorenal Med.* 2020;10(3).
doi: 10.1159/000505286
21. Armour JA. Functional anatomy of intrathoracic neurons innervating the atria and ventricles. *Heart Rhythm.* 2010;7(7):994-996.
doi: 10.1016/J.HRTHM.2010.02.014
22. Armour JA. Cardiac neuronal hierarchy in health and disease. *Am J Physiol Regul Integr Comp Physiol.* 2004;287(2):R262-R271.
doi: 10.1152/ajpregu.00183.2004
23. Shivkumar K, Ardell JL. Cardiac autonomic control in health and disease. *J Physiol.* 2016;594(14):3851-3852.
doi: 10.1113/JP272580
24. Meng L, Shivkumar K, Ajjola O. Autonomic Regulation and Ventricular Arrhythmias. *Curr Treat Options Cardiovasc Med.* 2018;20(5):38-.
doi: 10.1007/s11936-018-0633-z
25. Hanna P, Rajendran PS, Ajjola OA, *et al.* Cardiac neuroanatomy - Imaging nerves to define functional control. *Auton Neurosci.* 2017;207:48-58.
doi: 10.1016/J.AUTNEU.2017.07.008
26. Giannino G, Braia V, Griffith Brookles C, *et al.* The Intrinsic Cardiac Nervous System: From Pathophysiology to Therapeutic Implications. *Biology.* 2024;13(2):105.
doi: 10.3390/BIOLOGY13020105
27. Patsy M, Ge K, Khodabukus A, Bursac N. Development and modeling of cardiac autonomic innervation. *Nat Cardiovasc Res.* 2025;4(12):1598-1615.
doi: 10.1038/s44161-025-00746-7
28. Li YL. Stellate Ganglia and Cardiac Sympathetic Overactivation in Heart Failure. *Int J Mol Sci.* 2022;23(21):13311.
doi: 10.3390/IJMS232113311
29. Vaseghi M, Zhou W, Shi J, *et al.* Sympathetic innervation of the anterior left ventricular wall by the right and left stellate ganglia. *Heart Rhythm.* 2012;9(8):1303-1309.
doi: 10.1016/j.hrthm.2012.03.052
30. Higgins CB, Vatner SF, Braunwald E. Parasympathetic Control of the Heart. *Pharmacol Rev.* 1973;25(1):119-155.
doi: 10.1016/s0031-6997(25)06588-3
31. Herring N, Cranley J, Lokale MN, *et al.* The cardiac sympathetic co-transmitter galanin reduces acetylcholine release and vagal bradycardia: Implications for neural control of cardiac excitability. *J Mol Cell Cardiol.* 2012;52(3):667-676.
doi: 10.1016/j.yjmcc.2011.11.016
32. Shanks J, Herring N. Peripheral cardiac sympathetic hyperactivity in cardiovascular disease: role of neuropeptides. *Am J Physiol Regul Integr Comp Physiol.* 2013;305(12):R1411-R1420.
doi: 10.1152/ajpregu.00118.2013
33. Jani N, Weperen V Van, Emamimeybodi M, *et al.* Neuropeptide Y Receptor Inhibitor Enhances Effects of Vagal Nerve Stimulation and Reduces Effects of Sympathetic Activation: Assessments Using Real-Time Electrophysiological and Myocardial Neuropeptide Measurements. *J Am Coll Cardiol.* 2023;81(8):55.
doi: 10.1016/S0735-1097(23)00499-0
34. Chottová Dvoráková M, Wiegand S, Pesta M, *et al.* Expression of neuropeptide Y and its receptors Y1 and Y2 in the rat heart and its supplying autonomic and spinal sensory ganglia in experimentally induced diabetes. *Neuroscience.* 2008;151(4):1016-1028.
doi: 10.1016/j.neuroscience.2007.07.069
35. Jönsson-Rylander AC, Nordlander M, Svindland A, Ilebekk A. Distribution of neuropeptide Y Y1 and Y2 receptors in the postmortem human heart. *Peptides.* 2003;24(2):255-262.
doi: 10.1016/S0196-9781(03)00041-X
36. Sharma S. Morphometric interpretation of postganglionic sympathetic neurons that innervate myocardium. *bioRxiv.* Preprint posted online July 29, 2025.
doi: 10.1101/2025.07.27.667010
37. Meng X, Murali S, Cheng YF, *et al.* Increasing the expression level of ChR2 enhances the optogenetic excitability of cochlear neurons. *J Neurophysiol.* 2019;122(5):1962.
doi: 10.1152/jn.00828.2018
38. Ripplinger CM. Neural Regulation of Cardiac Rhythm. In: *Cardiovascular Signaling in Health and Disease.* International Publishing Springer; 2022:323-340.
doi: 10.1007/978-3-031-08309-9_11
39. Ramirez RJ, Ajjola OA, Zhou W, *et al.* A new

- electrocardiographic marker for sympathetic nerve stimulation: modulation of repolarization by stimulation of stellate ganglia. *J Electrocardiol.* 2011;44(6):694-699.
doi: 10.1016/J.JELECTROCARD.2011.07.030
40. Ajjola OA, Lux RL, Khahera A, *et al.* Sympathetic modulation of electrical activation in normal and infarcted myocardium: implications for arrhythmogenesis. *Am J Physiol Heart Circ Physiol.* 2017;312(3):H608-H621.
doi: 10.1152/AJPHEART.00575.2016
41. Ajjola OA, Yagishita D, Patel KJ, *et al.* Focal myocardial infarction induces global remodeling of cardiac sympathetic innervation: neural remodeling in a spatial context. *Am J Physiol Heart Circ Physiol.* 2013;305(7):H1031-H1040.
doi: 10.1152/AJPHEART.00434.2013
42. Zhang X, Shi T, Holmberg K, *et al.* Expression and regulation of the neuropeptide Y Y2 receptor in sensory and autonomic ganglia. *Proc Natl Acad Sci USA.* 1997;94(2):729.
doi: 10.1073/pnas.94.2.729
43. Jani NR, Van Weperen VYH, Ayagama T, *et al.* Sympathovagal crosstalk: Y2-receptor blockade enhances vagal effects which in turn reduce NPY levels via muscarinic receptor activation. *Cardiovasc Res.* 2025;121(14):2189-2203.
doi: 10.1093/cvr/cvaf180