



Pradeep S. Rajendran, Rosemary C. Challis, Charless C. Fowlkes, Peter Hanna, John D. Tompkins, Alon Greenbaum, Ken Y. Chan, Benjamin E. Deverman, Jeffrey L. Ardell, Viviana Gradinaru & Kalyanam Shivkumar

¹Cardiac Arrhythmia Center and Neurocardiology Research Program of Excellence, University of California - Los Angeles, CA; ²Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA; ³Department of Computer Science, University of California - Irvine, Irvine, CA

Abstract

Heart rate is under the precise control of the autonomic nervous system. However, the wiring of peripheral neural circuits that regulate heart rate is poorly understood. Here, we develop a clearing-imaging-analysis pipeline to visualize innervation of intact hearts in 3D and employed a multi-technique approach to map parasympathetic and sympathetic neural circuits that control heart rate in mice. We identify cholinergic neurons and noradrenergic neurons in an intrinsic cardiac ganglion and the stellate ganglia, respectively, that project to the sinoatrial node. We also report that the heart rate response to optogenetic versus electrical stimulation of the vagus nerve displays different temporal characteristics and that vagal afferents enhance parasympathetic and reduce sympathetic tone to the heart via central mechanisms. Our findings provide new insights into neural regulation of heart rate, and our methodology to study cardiac circuits can be readily used to interrogate neural control of other visceral organs.

Tissue clearing and computational pipeline to assess cardiac innervation





Identification of peripheral neural circuits that regulate heart rate using optogenetic and viral vector strategies











Acknowledgments

We thank the entire Shivkumar and Gradinaru Labs for helpful discussions. This work is supported by NIH Stimulating Peripheral Activity to Relieve Conditions (SPARC) Grant 10T20D023848-01 (K.S., V.G.). P.S.R. is supported by NIH National Heart, Lung and Blood Institute (NHLBI) Grant 5F31HL127974.



stimulation of the vagus nerve displays different temporal characteristics.

Vagal afferents enhance parasympathetic and reduce sympathetic efferent outflow to the heart via central mechanisms.