EDITORIAL

Cardiac autonomic control in health and disease

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Cardiovascular diseases are the leading cause of morbidity and mortality worldwide (Mozaffarian *et al.* 2015; Oliveira *et al.* 2015). What is becoming increasingly self-evident is that the progression of cardiovascular disease is dependent upon the interplay between the autonomic nervous system and the peripheral target tissues it regulates (Chen *et al.* 2014; Florea & Cohn, 2014; Fukuda *et al.* 2015). It is further recognized that there are inherent (e.g. genetic) and acquired factors (e.g. myocardial infarction) that impact the disease process (Zucker *et al.* 2012; Fukuda *et al.* 2015). Anatomical structure sets the foundation for function and a thorough understanding of these relationships, from the subcellular to integrated whole body neurohumoral control, is required for the development of cardiovascular therapies that have a strong mechanistic foundation.

Neuromodulation-based therapeutics for cardiovascular disease is an evolving science with profound implications for management of cardiac arrhythmias, heart failure and hypertension. Cardiac sympathetic denervation/decentralization (Bourke *et al.* 2010; Vaseghi *et al.* 2014) and bioelectric medicine (De Ferrari, 2014; Buckley *et al.* 2015; Zipes, 2015) targeted to 'nexus points' of the cardiac nervous system have already shown significant therapeutic promise. The importance of this area of science was the impetus for us to host the UCLA Autonomic Nervous System Control of the Heart in Health and Disease Symposium, first in 2012 and the second on 12 and 13 March 2015. These meetings were supported in part by the generous donations provided by the *Leonetti O'Connell Family Foundation*. The 2 day workshop had five major themes and 20 presentations. The themes were: (1) Functional Neuroanatomy of the Heart, (2) Neurohumoral Adaptations to Chronic Heart Disease, (3) The Role of the Autonomic Nervous System in Cardiac Arrhythmogenesis, (4) Pre-clinical Neurocardiology, and (5) Clinical Neurocardiology. For those interested in viewing specific presentations from these symposia, these can be found at http://dgsom.ucla.edu/streaming/cac-symposium/.

This special issue of *The Journal of Physiology* presents a synthesis of the primary themes, preclinical to clinical, that were brought forth in the 2015 meeting. It includes three white papers that summarize the current state of understanding for 'Molecular and Cellular Neurocardiology' (Habecker *et al.* 2016), 'Translational (pre-clinical) Neurocardiology' (Ardell *et al.* 2016), and 'Clinical Neurocardiology' (Shivkumar *et al.* 2016). These white papers represent the combined efforts of 39 leading international experts in the field and highlight the cellular, organ level and clinical aspects of neurocardiology. They summarize data derived from normal and pathological states. These papers also provide mechanistic insights into several emerging applications of autonomic regulation therapy for cardiovascular diseases.

In addition to the three white papers in this issue there is a special editorial on 'Neurocardiology – a neurobiologist's perspective' by Professor Jänig (2016). There are additional papers focusing on major aspects of autonomic neural processing and the neural–cardiac interface in normal and pathological states. At the level of the cardiomyocyte, alterations in excitation-contraction coupling, substrate utilization and receptor signalling are considered in normal *vs.* pathological conditions (Gloschat *et al.* 2016). At the level of peripheral autonomic ganglia, alterations in cyclic nucleotide pathways are discussed in relation to neurotransmitter release (Kalla *et al.* 2016; Li & Paterson, 2016). Consequences for peripheral neural network control of cardiac electrical and mechanical function is presented with a primary focus on neural transduction of cardiac pathology relative to heart failure and arrhythmias (Ardell *et al.* 2016). Relevant aspects of spinal cord, brainstem and higher centre processing are also brought to the forefront, especially as they relate to 'interoception' (Shivkumar *et al.* 2016). This series of papers also highlights many important aspects of cardiac control that are conserved across species or not (Gloschat *et al.* 2016). Ultimately our objective is to translate these findings to the human conditions. It is also critical for future studies to deploy existing methodologies in a physiological context (Joyner, 2016) and to evolve new biomarkers for assessing disease state and therapeutic interventions.

While it is always tempting to simplify regulation for system analysis, the evolving history of neurocardiology repeatedly demonstrates that the processing capabilities of the autonomic nervous system starting from neural networks on the heart and continuing all the way to subcortical regions are quite complex and nuanced. Sensory transduction is a fundamental link that traverses all levels of the neuraxis and ultimately translates into closed-loop reflex control of the heart. Alterations in neural processing and amplification of sympathoexcitation arising as a result of the transduction and transmission of afferent impulses from the peripheral to the central aspects of the cardiac nervous system are a major cause of cardiovascular disease progression (Ardell *et al.* 2016; Habecker *et al.* 2016; Shivkumar *et al.* 2016). Evolving new therapeutic approaches to manage such neural and cardio-neural substrate changes is a major impetus for this field.

In conclusion we hope that many more curious and bright minds will enter this field and also learn to embrace its complexity. The multi-disciplinary approaches that are outlined in this issue point to a new therapeutic dimension. Neuromodulation-based strategies provide unique opportunities to develop meaningful therapies for the tens of millions who are going to die suddenly from arrhythmias or suffer serious morbidity and ultimate death due to heart failure in the coming years!

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The Journal of Physiology

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Additional information

Competing interests

None declared.

Author contributions

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