

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Editorial

Special issue, 'Circadian Rhythms: Autonomic & Endocrine Function in Health and Disease'



“Physiological rhythms are central to life. Some rhythms are maintained throughout life, and even a brief interruption leads to death. Other rhythms, some under conscious control and some not, make their appearance for various durations during an individual's life. The rhythms interact with one another and with the external environment. Variations of rhythms outside of normal limits, or appearance of new rhythms where none existed previously, is associated with disease.” Leon Glass and Michael C. Mackey, *From Clocks to Chaos: The Rhythms of Life*, Princeton University Press, 1988

Circadian rhythms reflect the optimization of biological performance with respect to the 24 h light-dark cycle on planet Earth. They are observable across a variety of organisms over a range of organisational levels; e.g., gene expression at the cellular level to the nervous and endocrine control of complex multicellular organisms. In animals chronobiology has demonstrated that behaviour and internal organ function is under circadian control enabling living creatures to optimize system performance thereby maximizing species' survival and evolution. By focusing on autonomic and endocrine function in health and disease this Special Issue aims to provide readers with insights into circadian rhythms of life that involve whole body (including CNS) physiology and, organs and cells fulfilling specific roles. It is clear that the disruption of circadian rhythms consequent to 21st century living styles, in so-called developed countries, can trigger/cause disease. Clock genes are ubiquitous and therefore research into the roles of entrainment of peripheral clocks by the master clock in the suprachiasmatic nucleus (SCN: feedforward), the within organ interaction of cellular clocks (e.g., coupling) and feedback influences on the master clock arising from external and internal sources (including peripheral clocks) is central to understanding the factors which determine function in health and disease.

Buijs et al., in their article entitled: “The suprachiasmatic nucleus; a responsive clock regulating homeostasis by daily changing setpoints of physiological parameters”, consider how the SCN (the master clock) adjusts physiological setpoints in line with the 24 h light-dark cycle and other external and internal challenges. In doing so their overview provides an ideal background for the more specialised reviews contained within this Special Issue. Effective circadian control is dependent upon the master clock receiving information from a diversity of CNS areas, from other internal organs and the external environment. They consider the various feedback and feedforward mechanisms and discuss how disease may be caused/triggered by frequent disruption of circadian physiology; e.g., shiftwork and night eating. They also consider the role of peripheral clock genes in circadian rhythm generation.

Henrik Oster & colleagues concentrate on some of the issues introduced by Buijs and colleagues. In their review they focus on the

circadian regulation of the three major hormonal axes arising in the hypothalamus, relayed by the pituitary and terminating in: the adrenal (HPA axis); thyroid (HPT axis); the gonads (HPG axis). They explore the roles of the master clock in the SCN, peripheral tissue clocks and feedback mechanisms in rhythm generation. They consider the nature of circadian rhythms in these systems, their interactions and influences on target organ functions, and effects on these rhythms caused by disruptions to the light-dark cycle and food intake plus disturbances caused by disease processes. It is important to note that many practices associated with modern day living impact on glucocorticoid (GC) rhythms; e.g., high-speed travel across time zones and shift work. Oster and colleagues importantly note that GC is vital to the synchronisation of circadian rhythms across organ systems and that there is a link between GC arrhythmicity and diseases (e.g., depression and metabolic disorders). The authors highlight the observation that genetic clock gene variants are also associated with a broad range of diseases (e.g., neurodegenerative disorders, diabetes, and affective disorders). In their review Baschieria and Cortelli pursue the theme of neurodegenerative diseases in relation to circadian cardiovascular function.

Circadian control of adipose tissue function and whole body energy homeostasis are the topics explored in the review by Lekkas & Paschos. They reflect on the various components of control (master clock, peripheral clocks, communication between clocks and adipose tissue endocrine function), adipose tissue types and note that white type adipose tissue has been investigated the most. The function of adipocyte circadian clock genes in differentiation is a major topic for discussion. The control of key enzymes involved in lipogenesis and lipolysis is core to the ability of an organism to respond to diurnal variations in energy demands and availability; SCN is involved in this regulation through both autonomic and endocrine control. As highlighted by Buijs et al., in their review effective circadian control involves signals emanating from peripheral organs; adipokines are secreted from adipose tissue to influence food intake, storage and consumption. Although diurnal variation in plasma adiponectin and leptin has been described more research is required regarding the mechanisms involved. With regard to the food intake side of energy availability Lekkas & Paschos highlight the complexity of control; although the masterclock is involved they emphasise the importance of feedback from adipose tissue, behavioural, environmental and reward elements.

The circadian control of cardiovascular function is notable and involves both nervous and endocrine regulation. In healthy individuals who have a normal sleep-wake cycle arterial blood pressure is characterized by an on average 10-20% fall during the night (nocturnal dip) compared with day time average. Average heart rate decreases during the night with heart rate determined by the stage of sleep: both tachycardia and bradycardia are observed during sleep. Baschieria and Cortelli discuss such circadian-related modulations of cardiovascular

<https://doi.org/10.1016/j.autneu.2019.102562>

performance in their article: “Circadian rhythms of cardiovascular autonomic function: Physiology and clinical implications in neurodegenerative diseases”. They describe the underlying mechanisms of this control, nervous and endocrine involvement, including central and peripheral circuitry. Techniques for monitoring cardiovascular variables are described and the relationship between certain neurodegenerative diseases and loss of circadian cardiovascular rhythms are considered.

David Pollock and colleagues consider the contribution of renal function to circadian related changes in blood pressure in their article: “Autonomic Nerves and Circadian Control of Renal Function”. They consider the effects of renal denervation (humans and other animals), afferent and efferent renal nerve activity, the impact of salt load and timing of salt intake, and chronic kidney disease. They review evidence that supports the idea that chronotherapy can improve the efficacy of antihypertensive treatments. Furthermore, they review studies that have investigated the impact of the timing of food intake, salt intake and high fat diet on arterial blood pressure and its circadian rhythmicity. Finally the authors state: “There is a paucity of specific information available that defines the relationship between autonomic control of kidney function and circadian rhythms” and that further studies in the area may lead to improved therapeutic strategies.

Todd and Machado in their review explore the link between the circadian control of behaviour (in particular aggression) and autonomic control. They consider the involvement of a suprachiasmatic, supra-ventricular zone, ventromedial hypothalamus relay (SCN → SPZ →

VHM) and associated pathways in this regulation. They return to an issue considered by Bascieria and Cortelli focussing on neural disorders characterized by aggressive behaviour, and circadian and autonomic dysfunction. They note that pathological aggression is associated with aberrant autonomic control, that SCN → SPZ → VHM disruption leads to increased behavioural aggression (in their animal model) which is temporally aligned to sundowning syndrome observed in patients with Alzheimer's disease and related dementias. Such patients also suffer from disturbances of autonomic control, as do those with other behavioural disorders.

The organisms that live on planet Earth are “tuned” to its natural cycles; e.g., the seasons, lunar cycles and 24 h light-dark cycles. There is now evidence that physiological setpoints vary with such cycles. This Special Issue has provided some insights into how our understanding of circadian control has advanced over recent years. We are now beginning to understand how disruption of biological clocks, by factors relating to some modern lifestyles, can lead to increased morbidity and how chronobiology can be used to improve quality of life and therapeutic strategies. The disruption of circadian rhythms (e.g., by light pollution) threatens the wellbeing of many living creatures, not just humans, and therefore the survival of species.

Michael P. Gilbey
Department of Neuroscience, Physiology & Pharmacology, UCL (University College London), London, UK
E-mail address: m.gilbey@ucl.ac.uk.