Neurons and biological timing

https://www.neurodegenerationresearch.eu/survey/neurons-and-biological-timing-2/

Principal Investigators

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Country

United Kingdom

Title of project or programme

Neurons and biological timing

Source of funding information

MRC

Total sum awarded (Euro)

€ 7,771,965

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01/10/2011

Total duration of award in years

5.0

The project/programme is most relevant to:

Neurodegenerative disease in general

Keywords
Research Abstract

Our daily rhythms of sleep and wakefulness, hormone secretion and metabolic activity are driven by the brain’s circadian pacemaker: the suprachiasmatic nucleus (SCN) of the hypothalamus. These rhythms dominate the pattern of our lives and set the tempo of Society. Disruption of circadian structure underlies, or is associated with, many major contemporary health problems, including sleep disorders, metabolic syndrome, dementia and psychiatric illness. The current molecular model of the circadian oscillator within the SCN is one of interlocked transcriptional/post-translational feedback loops, which sustain autonomous 24 h

cycles of gene expression. Notwithstanding its success, our knowledge of its components is far from complete and the model is heavily based on evidence and inferences of the properties and behaviour of clock factors in heterologous systems, far removed from the SCN. Our objective, therefore, is to conduct a series of definitive experiments to identify novel components of the SCN clockwork, define their activities in relation to known SCN properties and thereby expand, correct and enhance the current model. We aim to identify how daily time is defined both at the level of individual SCN neurons and across the SCN circuit. Moreover, we shall explore how this central time-keeper co-ordinates subordinate circadian clocks across the brain and thus consolidates the cycle of sleep and wakefulness. Technically, we shall develop and exploit a combination of neurobiological, molecular genetic, biochemical and behavioural approaches, both in vitro and in vivo. An important feature is extensive use of genetically modified mice. These are used for fluorescent and bioluminescent real-time imaging of circadian gene and protein expression in organotypic cultures of SCN. Some mice carry targeted or random mutations of clock genes whilst others act as genetic models of diseases with a pronounced circadian disturbance. As a test of our evolving models of cell-autonomous and circuit-level timekeeping, it should be possible to accelerate or slow down the clock, to control circadian phase, and indeed to stop and start the cycle at will, by temporally regulated expression of core components of the loop and inter-neuronal signalling pathways. The second aim of the work will be to elucidate the molecular and cellular mechanisms downstream from the core oscillator that are responsible for circadian regulation of SCN targets in the brain, and thence to peripheral, tissue-based clocks. Finally, with growing knowledge of circadian molecular neuroBiology, it will be possible to explore the relevance of circadian timing to neurological disease, in particular by examining circadian function in animal models of such diseases, including Huntingtons disease (HD) and Alzheimers disease (AD), as well as disorders arising from genetic (several sleep disorders) or environmental (e.g. shift-work) disturbance of circadian physiology. It is in this regard that new knowledge of the circadian timing system offers considerable scope for translational development.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Neurodegenerative disease in general

Years:
2016

Database Categories:
N/A

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N/A