MICRA Seedcorn Application 2014

Project Title: Does exercise intervention influence age-associated miRNA signatures of the brain regions regulating cognition and biological timing?

Applicants and contact details

Dr. Qing-Jun Meng, MRC Career Development Award Fellow in Circadian Biology, Faculty of Life Sciences, University of Manchester

Dr. Vanja Pekovic-Vaughan, Wellcome Trust Fellow in Musculoskeletal Biology, Institute of Ageing and Chronic Disease, University of Liverpool

Dr. Daryl Shanley, Director of Centre for Integrated Systems Biology of Ageing and Nutrition (CISBAN), Institute of Ageing and Health, University of Newcastle-upon-Tyne

Background

Age is a major risk factor for the most common neurodegenerative diseases, including Alzheimer's, cerebrovascular and Parkinson's disease, which present a major area of unmet clinical need in the UK and globally. Exercise has been recognized as an important protective factor reducing disability and mortality, and has become a focus of healthy brain aging as well as impairments in cognition and sleep. One molecular mechanism by which exercise is proposed to positively influence healthy ageing is through up-regulating the mechanisms related to biological (circadian, or 24 hourly) timing. Circadian clock is a fundamental timing system which is conserved across all species, including humans, and is central in maintenance of health and well-being. Many aspects of mammalian physiology are governed by the circadian clock, including sleep quality, hormonal release and cognitive functions such as memory, mood and learning. Intense research in understanding circadian timing mechanisms has been fuelled by the discoveries that genetic and environmental disruptions of circadian rhythms (e.g. mutations, ageing, shift work, pollution) lead to a decline in the activity of the circadian system and are associated with a host of age-related pathologies and neurological disorders.

The circadian clock is organized hierarchically. The central or master circadian clock is located in the suprachiasmatic nuclei (SCN) of the brain's anterior hypothalamus. SCN neurons are reset daily by environmental light and are responsible for sending timing information to the other brain regions as well as peripheral tissues. Emerging studies have focused on clock gene oscillations in other brain regions, including those involved in memory processing and cognition such as the hippocampus. Recent work has revealed that hippocampal oscillations are maintained by the cyclic outputs from the SCN, and that critical signaling events in the hippocampus required for memory consolidation and learning depend on gene oscillations in the SCN.

Work leading to this proposal

Our recent work has focused on deciphering age-related molecular changes in the clock gene rhythms of SCN neurons and peripheral tissues in mice. These studies identified advanced timing of the SCN rhythms and altered phase relationships with some of the tissues in the body, suggesting temporal misalignment of the pathways regulating inter-tissue synchronisation. Our molecular findings corroborate previous observations of altered rhythms of behaviour, sleep-wake cycles and earlier onset of sleep in aged individuals.

Recent work has focused on epigenetic mechanisms, including microRNAs, as potential interface between the circadian clock and inter-tissue communication in health and disease. Indeed, our transcriptome profiling studies identified a cluster of brain-specific pre-microRNA precursors that show altered expression during ageing. Using bioinformatic approaches, we find that some of the miRNA targets altered in aged SCN have potential roles in memory pathways.

Research plan and Impact

Through this seedcorn application, we propose to undertake further identification and characterisation of the mature miRNAs and their target genes in the SCN (Dr Meng) and hippocampus in aged model organisms before and after adaptation to exercise (Dr Pekovic-Vaughan). The findings from these data will be used in combination with mathematical modelling and system-level analyses of the brain (Dr Shanley). This proposal will allow us to build on our current observations and exploit the varied expertise within this team to foster interdisciplinary research on the biology of healthy brain ageing. This knowledge will provide comprehensive understanding of the dynamic epigenetic processes involved in health-promoting effects of physical activity on the brain homeostasis. The investigation of these mechanisms is important because circadian rhythm disturbances have been implicated in determining disease outcomes in several neurodegenerative diseases, and exercise is one of the main effective interventions for promoting healthy brain ageing.