Project Details	
Project Code	MRCNMH26Br Chrobok
Title	Chrono-nutrition and Chrono-pharmacology: Investigating the Impact of Intermittent Fasting and Timed Pharmacological Treatments for Obesity Management
Research Theme	NMH
Project Type	Wet lab
Summary	Most physiological processes, including feeding, follow circadian (~24h) cycles. In mammals, these rhythms are generated by endogenous 'body clocks' within the brain. Dysfunction of these body clocks can contribute to obesity and other metabolic disorders. Our studies focus on a site in the brainstem that controls appetite, which we have discovered also has robust circadian timekeeping. This project aims to understand how these daily rhythms in the brainstem satiety centre can be harnessed to formulate more effective strategies and treatments for tackling obesity.
Description	Life on Earth is subordinate to periodic alterations in the environment, with the most notable changes seen from day to night. To adapt to these cyclic changes, living organisms evolved endogenous 24h timekeeping mechanisms named circadian clocks. In mammals, the suprachiasmatic nuclei (SCN) are conceived as the primary clock, but rhythmic clock gene expression occurs in extra-SCN brain structures and many peripheral tissues, indicating that rhythmic control of homeostasis is devolved to these local clocks. However, the regulation of these rhythms by environmental cues and lifestyle has not been fully understood. Obesity stands as a formidable public health burden, with about a quarter of the UK adults living with obesity and comorbidities. These include an increased risk of chronic conditions such as diabetes, cardiovascular diseases, and certain cancers, as well as a negative impact on mental health. Tackling obesity demands a comprehensive approach, involving public health initiatives, education, and policy changes to promote healthier lifestyles. Recent advances in circadian neuroscience highlight the importance of food and feeding time as a cue synchronising our body clocks. Additionally, restricting food to a narrow window during the day (e.g., intermittent fasting) proves beneficial for general health and well-being, including management of weight, cardiovascular health, and diabetes. Various pharmacotherapeutic agents, including glucagon-like peptide-1 receptor (GLP-1R) agonists, have been investigated for their efficacy in weight reduction. However, challenges persist in terms of long-term sustainability, side-effect profiles, and patient adherence. This project aims to investigate the effects of intermittent fasting and pharmacological treatments of obesity (e.g., GLP-1R antagonists) on the timekeeping properties of extra-SCN oscillators in the mouse brain. It also aims to establish the best time of day for obesity drug treatment and the potential influence of meal timing on their effectiveness. The student will utilise cutting-edge experimental techniques in circadian neuroscience, including: (1) fluorescent in situ hybridisation and confocal microscopy to investigate molecular rhythms in vivo (e.g., clock gene expression); (2) real-time monitoring of clock gene expression ex vivo using PERIOD2::LUCIFERASE reporter mice;

	(3) electrophysiological recordings ex vivo on multi-electrode arrays over 24h; (4) automated monitoring of feeding, drinking, and wheel running in home cages; (5) range of molecular methods used for quantitative assessment of gene expression. The student will receive comprehensive training in in vivo physiology and will obtain a Home Office animal licence. Additionally, to support the development of advanced data analysis skills, they will attend coding courses (e.g., R, Python, MatLab). During the project, they will have a chance to travel between Bristol and Exeter to explore the experimental potential of the laboratories of all three supervisors. Initially, the PhD student will focus on characterising the 24h rhythms in GLP-1 receptor expression in the DVC in the DVC. They will investigate using molecular and electrophysiological methods, laying the foundations for their in vivo studies. Then, based on already obtained data, the student's interest, and results of their experiments, they can choose which different in vivo and behavioural models to explore. This gives the student the possibility to take control over the project and introduce their own ideas and directions. Ultimately, they will aim to understand what is the best circadian time for treatment with GLP-1 mimetics, and how this can be set up by diet; all through the lens of the circadian rhythms in the brainstem satiety centre.
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