Project Details	
Project Code	MRCNMH24Br Chrobok
Title	Cannabinoids in the ticking network of the brainstem satiety centre
Research Theme	Neuroscience & Mental Health
Summary	Most physiological processes including feeding follow circadian (~24h) cycles generated by body clocks within the brain, which dysfunction contributes to obesity and other metabolic disorders. Our studies focus on circadian timekeeping in the brainstem centre which limits food intake. This project aims to understand how cannabinoids, known to promote appetite, impact cell-cell communication and the timing of feeding via the activity of this brainstem satiety centre.
Description	Life on Earth is subordinate to periodic alterations in the environment, with most notable changes seen from day to night. To react, anticipate, and 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. The dysregulation of circadian rhythmicity seen in the modern 24/7 society leads to obesity, cardio-vascular problems, metabolic syndrome, and some kinds of cancer, constituting a major public health burden. Therefore, it is important to understand the inner workings of these extra-SCN oscillators, and to determine their contribution to circadian physiology and behaviour. Cannabinoids and endocannabinoids have been the focus of many studies regarding their clinical applicability for pain management and their appetite promoting actions. Cannabinoid receptors are sparsely expressed in the SCN; however, their activation modulates clock responses to light. Interestingly, high expression of cannabinoid receptors was found in the brainstem satiety centre. Recently, we found that this brainstem satiety centre – the dorsal vagal complex (DVC) has exceptionally robust timekeeping properties which are sensitive to diet. Moreover, we characterised rhythmic expression of genes encoding many neurotransmitter receptors in the DVC, including glutamatergic, GABAergic, and cannabinoid receptors. This implies, that the DVC clock may modulate the strength of synaptic transmission over 24h, therefore filtering incoming information e.g., from the gastrointestinal system. Studying functional and behavioural consequences of circadian rhythmicity in synaptic transmission of DVC neurons has clear physiological and clinical implications for our understanding of feeding behaviour and the development of obesity. The aim of this project is to explore circadian timekeeping in the brainstem and characterise daily rhythms in synaptic transmission of the DVC and its modulation by cannabinoids. The student will receive comprehensive training in in vivo physiology and will obtain 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 the student will have opportunities to travel between Bristol and Exeter to explore experimental potential of laboratories of all three supervisors. The PhD student will explore synaptic transmission of DVC neurons using: - ex vivo electrophysiological techniques (multi-electrode arrays,

	patch clamp) combined with targeted pharmacology; - real time ex vivo bioluminescence recordings of clock gene expression in slice cultures; - immunohistochemistry and fluorescent hybridisation in situ (RNAscope) for the co-localisation of chosen clock genes and synaptic receptors; - monitoring of home cage behaviour with automated recording of food and water intake, and running wheel activity; - quantitative analysis of electrophysiological signal in MatLab and Python, and complex statistical models in R and MatLab. Initially, the PhD student will focus on characterising the role of cannabinoid receptor 1 (Cnr1) activation over 24h in the DVC. They will investigate its effects on synaptic transmission, clock gene expression, and ingestive behaviour. Then, based on transcriptomic data already available in the lab, the student's interest, and results of their experiments, they can choose which different aspects of synaptic transmission 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 build a model of circadian modulation of synaptic transmission in this brainstem satiety centre.
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