| Project Details | |
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| Project Code | MRC23NMHBr Ambler |
| Title | Turn it off and on again - exploiting brain hibernation circuits to improve outcomes in critical illness |
| Research Theme | Neuroscience and Mental Health |
| Summary | Torpor (a brief hibernation) is a remarkable phenomenon exhibited by many animals. It is characterised by extreme physiology including lowered body temperature and heart rate, and immune modulation. As a protective state, torpor is of interest for many clinical and space medicine applications. This project will use mice to characterise the brain circuits that generate each physiological component of torpor to identify potential targets for human medicine and beyond. |
| Description | Torpor is a protective strategy adopted by many species (including mice) to conserve energy during environmental challenge e.g., low ambient temperature, food shortage, or illness. Using cutting edge neuroscience techniques, the project will explore the brain mechanisms controlling this unique state. Knowledge gained might lead to the development of new therapies that allow critically ill patients to better tolerate organ dysfunction, or to protect humans against the challenges of long-distance space travel. Torpor has three important components: reduced body temperature and oxygen consumption; reduced heart rate & cardiac output; and immune modulation such that animals tolerate rather than resist infection. Work from our lab (DOI: 10.1523/JNEUROSCI.2102-21.2022) and elsewhere, including two recent Nature publications (DOI: 10.1038/d41586-020-01600-5), identified neurons in an area of the brain called the preoptic area of the hypothalamus (POA) that are active during torpor in mice. When reactivated, these neurons reproduce elements of torpor. However, the precise characteristics of these POA neurons, and the organisation of the brain circuits mediating these dramatic physiological adaptations remain to be defined. We believe subsets of torpor-inducing neurons in the POA project to distinct brainstem regions to generate the different components of torpor. We hypothesise that: POA to dorsomedial hypothalamus and/or raphe connections reduce body temperature; POA to nucleus accumbens connections reduce heart rate; and POA to the dorsal vagal complex connections modulate immune function. By understanding the mechanisms of natural torpor, we aim to identify conserved brain circuits in species for which it is not a natural behaviour (e.g., rats or even humans). Proof-of-concept experiments in rats have demonstrated that activating these brain circuits reduces body temperature, heart rate, and oxygen consumption. These might form therapeutic targets to generate synthetic torpor-like states, which could be exploited to benefit patients. Research question: Does a single population of neurons generate all the physiological adjustments associated with torpor (i.e., a torpor master switch)? or do distinct POA subpopulations control different components via projections to specific downstream nuclei? Aim: To characterise the torpor-inducing circuits in the mouse brain. Objectives: • Use genetic tracing and activity dependent targeting to label ('TRAP') downstream projections from POA neurons that are active during torpor. • Use intersectional chemogenetics and activity-dependent TRAPing to explore the function |

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| | of specific projections from torpor-inducing neurons in the POA to downstream targets. This will include physiological assessment of cardiorespiratory function, body temperature, and immune cell regulation. • Perform single nucleus RNA sequencing to phenotype POA torpor-inducing neurons, perform cluster analysis of these neurons, and correlate this with the anatomical targets to which they project. The student will receive training and support from a highly experienced supervisory team from Bristol and Exeter. They will be trained and supported to take ownership of the project. Based on pilot studies and literature review, the student will steer the selection of candidate brain pathways for anatomical characterisation and RNA sequencing and can focus their studies on a specific component of the physiology e.g., body temperature, cardiovascular, and immune function. This research project will be part of a programme of torpor research that was recently funded by the MRC & BBSRC. The student will be embedded in the Anaesthesia, Pain, & Critical Care group in Bristol led by Prof Tony Pickering working within the team of Dr Mike Ambler (Clinical Lecturer in Intensive Care Medicine) with two post-doctoral researchers and with cross-GW4 supervision from Prof Kate Ellacott and Dr Rosemary Bamford in Exeter. |
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