Project Details	
Project Code	MRCNMH26Br Mastitskaya
Title	Brain-heart connections: how astrocytes shape the cardiovascular protective effects of GLP-1
Research Theme	NMH
Project Type	Wet lab
Summary	This PhD project will investigate how glucagon-like peptide-1 (GLP-1), a hormone central to metabolism, interacts with astrocytes – supportive "star-shaped" brain cells – to influence brain–heart communication. The project will employ cutting-edge techniques, including genetic targeting of specific brain cells, experimental models of heart attack, and advanced imaging, to explore how these pathways protect the heart. Conducted in collaboration with leading experts in Bristol and Exeter, the research will combine physiology, neuroscience, molecular biology, and data science. The findings aim to uncover new strategies to harness brain signals for heart protection and develop novel treatments for cardiovascular disease.
Description	The GLP-1 analogue drugs took the market by storm, promising magic cure for obesity. The main physiological role of endogenous gut-derived GLP-1 is the stimulation of insulin release from the pancreas in response to food intake. There is also brain-derived GLP-1 that targets neural circuits regulating satiety. Centrally produced GLP-1 and pharmacological GLP-1 receptor agonists have potent effects on the processing of autonomic reflexes in the brainstem. We have previously demonstrated that GLP-1 acts as a molecular factor of vagally mediated cardioprotection (PMID: 27702763). The vagus nerve is critically important in cardiovascular health. Vagus nerve stimulation reduces myocardial infarction (PMID: 22739118, PMID: 26918777), prevents the progression of heart failure and improves exercise capacity (PMID: 32875170). It is difficult to engage vagus nerve activity in patients of advanced age or in diabetes due to impairment of neural transmission in the heart. Therefore, targeting the downstream molecular events pharmacologically is the way to overcome these limitations. GLP-1 receptor agonists, such as Ozempic, have proven to be incredibly efficient in the treatment of diabetes, reducing body weight and minimising the other consequences of cardiometabolic disease. However, the exact location of the GLP-1 receptor and the molecular pathway(s) responsible for GLP-1's cardioprotective effects are not fully understood. We have preliminary data showing that GLP-1 protects the heart via modulation of autonomic reflexes at the level of the dorsal vagal complex (DVC) in the brainstem. There is also substantial experimental evidence suggesting a crucial role of brainstem astrocytes in the processing of cardiovascular reflexes (PMID: 32132265) and in the regulation of GLP-1R mediated effects on energy balance (PMID: 27013681). We will combine the expertise of the research groups in Exeter and Bristol to study the role of brainstem astrocytes in the cardioprotective effects of endogenous GLP-1 and GLP-1R agonists using rodent models. The project will involve state-of-the-art experimental techniques in neuroscience and cardiovascular physiology, including in vivo model of myocardial infarction, genetic targeting and manipulation of select

	populations of brainstem neurones and astrocytes, and cardiovascular phenotyping. The research aims of the project will include the following: 1) To characterise the cardioprotective effects and dose-response relationship of GLP-1R agonists administered systemically (i.v.) vs centrally (intracerebroventricular, i.c.v.) in an in vivo model of myocardial ischaemia/reperfusion injury. Pharmacological experiments will explore if CNS administered GLP-1R antagonists block cardioprotection evoked by systemically administered GLP-1R agonists and vice versa. 2) To determine the role of centrally produced endogenous GLP-1 in cardioprotection. The PPG neurones of the mouse brainstem will be ablated using Cre-dependent expression of diphtheria toxin fragment A (PMID: 30279161). 3) To study the effects of GLP-1R agonists and antagonists on neuro-glial communication in brainstem in the presence of various neuro- and gliotransmitters in electrophysiology and Ca imaging experiments. 4) The role of brainstem astrocytes in the cardiovascular effects of GLP-1R activation will be studied in experiments on their pharmacological inhibition (PMID: 27013681) or chemogenetic activation (PMID: 37370201). The student will receive comprehensive training in cardiovascular physiology and autonomic neuroscience, will become skilled in in vivo research and will obtain a Home Office animal licence. To support the development of data analysis skills they will enrol in coding courses in the first year of their PhD (R, Python, MatLab). The student will be encouraged to regularly engage in group meetings and research seminars both in Bristol and Exeter and will have the opportunity to work in both laboratories, in accordance with research needs, to benefit from the training and collaboration potential of the supervisory team. Informed by the outcome of each of the main research aims, the student can choose which aspects of GLP-1R mediated cardioprotection to explore. For example, if peripherally administered GLP-1R agonists mediate cardioprotection via activation of GLP-1Rs in the CNS, a student-led parallel line of research can explore the optimisation of timing and route of drug delivery, as well as the choice of the agonist to achieve the most potent anti-arrhythmic and cardioprotective effects. Upon reaching each milestone of the project, the student will also have the freedom to choose to learn and apply additional techniques, for example, spatial RNA profiling of the DVC upon peripheral vs central GLP-1R activation. This project will disentangle the cardiovascular effects of central GLP-1R activation and role of brainstem astrocytes in integration of cardioprotective reflexes. The findings of the studies will inform strategies on the therapeutic applications of GLP-1R agonists to improve cardiovascular outcomes in metabolic disease.
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