Institute: Institute of Zoology and Biomedical Research

Topic: Neuronal mechanisms of fear and anxiety control - the role of nucleus incertus to ventral hippocampus pathway in pattern separation, anxiety and contextual fear memory

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Background information:
Trauma and excessive stress can lead to maladaptive responsiveness to stressful situations that is strongly associated with anxiety disorders, including post-traumatic stress disorder (PTSD). The core of PTSD and many other anxiety disorders pathophysiology, are deficits in the processing of contextual information related to emotional memory and fear extinction. An important neuronal mechanism underlying the development of PTSD comprise impaired pattern separation, process that reduces overlap between patterns of neuronal activity representing similar experiences.
A principal brain structure implicated in the circuits controlling emotional behaviour and anxiety is the ventral hippocampus (vHipp) **(1)**. Notably, pattern separation is performed in the hippocampal dentate gyrus (DG), yet the precise neural circuits and molecular mechanisms involved in control of pattern separation remain unclear. Among the poorly understood, but key to contextual memory formation, is hippocampal innervation from the nucleus incertus (NI), the brainstem structure critically involved in control of anxiety behaviour, and the main source of relaxin-3 (RLN3) in the brain **(2)**.

The main question to be addressed in the project:
Despite emerging evidence of a role of vHipp and NI in the control of anxiety, the nature of NI input to vHipp, and an involvement of this innervation in shaping anxiety associated behaviours and pattern separation remain uncharacterised. Therefore, the major goals of the proposed research are to investigate the functional connectivity and neurochemical profile of the NI-vHipp axis, the role of this pathway and the RLN3/RXFP3 signalling in shaping vHipp neuronal activity, neuronal pattern separation and anxiety related behaviours.

Information on the methods/description of work:
In studies to elucidate the nature of the interaction between NI and vHipp at the cellular level, ex vivo multi-electrode array (MEA) of rat vHipp neuronal activity during optogenetic activation of NI originating fibres are planned. Moreover, MEA recordings will verify RLN3 actions on vHipp DG neurons and will determine the involvement of the RLN3/RXFP3 system in DG pattern separation. Multiplex in situ hybridization, immunohistochemical and neural tract-tracing studies in rats, will characterise the neurotransmitters and receptors expressed by neurons comprising the NI-vHipp pathway, as well as the origin of the RLN3 innervation of vHipp. Finally, behavioural experiments in rats using chemogenetics and intra-hippocampal RLN3 injections, will test the nature of the NI-vHipp pathway involvement in anxiety and contextual fear processing.

Additional information (e.g Special requirements from the student):
Candidates with previous experience in electrophysiological *ex vivo* MEA recordings, analysis of electrophysiological data, preparation of tissues for subsequent anatomical studies, *in situ* hybridization and immunohistochemical techniques.

Place/name of potential foreign collaborator:
Florey Institute of Neuroscience and Mental Health, Melbourne, Australia/Professor Andrew Gundlach

References:
[1] Jimenez, J. C. et al. Anxiety Cells in a Hippocampal-Hypothalamic Circuit. Neuron 97, 670-683.e6 (2018).
[2] Szőnyi, A. et al. Brainstem nucleus incertus controls contextual memory formation. Science 364, eaaw0445 (2019).