Institute of Zoology and Biomedical Research

**Topic:** The role of interpeduncular nucleus - nucleus incertus connection in novelty preference control

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**Background information (max 200 words):**

The ability to detect and correctly respond to novel stimuli is fundamental to survival, and atypical habituation and inappropriate responses to novelty are strongly related to a range of neuropsychiatric disorders, including autism, schizophrenia, attention-deficit-hyperactivity disorders (ADHD), addiction and anxiety disorders (1). Recently, a new, critical aspect of the neuronal mechanisms underlying novelty signalling was discovered. It was shown that the midbrain interpeduncular nucleus (IPN) and the medial habenula, together with and dopaminergic neurons in the ventral tegmental area, form a neuronal circuit crucial for optimal familiarity signalling and expression of novelty preference. Importantly, it is well established that IPN is strongly innervated by the nucleus incertus (NI), a stress-sensitive node of an ascending arousal network and a major source of relaxin-3 (RLN3) neuropeptide in the brain (2). Importantly, central activation of the RLN3 receptor, relaxin-family peptide receptor 3 (RXFP3), has been shown to modulate social interactions of treated rats with a novel conspecific and reduce elevated social anxiety in mice (3). Furthermore, neural tract-tracing and behavioural data clearly indicate that the IPN is strongly innervated by RLN3-containing NI nerve fibres and central activation of RXFP3 disrupts the capacity to express preference of novel over familiar stimuli in rats.

**The main question to be addressed in the project:**

Despite the emerging awareness of the NI-IPN connection to novelty preference signalling, the nature of NI neuronal inputs to IPN, as well as the role of NI in stress-related impairment of novelty preference remains unknown. Therefore, a major goal of the project is to investigate the functional connectivity and neurochemical nature of NI-IPN axis as well as the role of this pathway in novelty recognition in physiological and pathological (stressful) conditions. In particular, this project will aim to clarify the anatomical and neurochemical components involved in the action of RLN3 in the IPN to reveal the physiological role of RLN3/RXFP3 signalling in novelty preference and to assess the therapeutic potential of RXFP3-related treatments in related clinical conditions.

**Information on the methods/description of work:**

In studies designed to better understand the nature of the interaction between NI and IPN at a cellular and receptor level, whole-cell patch-clamp electrophysiological recordings of IPN neuronal activity during both optogenetic activation of fibres originating in NI, as well as neuropeptide-induced activation of IPN neurons were planned. Moreover, selective, optogenetic activation of medial habenula and ventral tegmental area axonal endings in the IPN, with simultaneous RXFP3 activation will answer the question regarding the involvement of RLN3/RXFP3 system in familiarity and novelty signalling, respectively. Multiplex in situ hybridization and neural tract-tracing studies will characterise the neurotransmitters and receptors expressed by neurons constituting the NI-IPN axis. Finally, behavioural experiments with the involvement of chemogenetics, will test the hypothesis that the NI is involved in IPN-controlled novelty/familiarity related behaviours and the NI has a role in stress-related impairment of novelty preference.

**Additional information (e.g Special requirements from the student):**

Candidates with previous experience in electrophysiological *ex vivo* recordings, analysis of electrophysiological data, preparation of tissues for subsequent anatomical studies and immunohistochemical techniques.

**Place/name of potential foreign collaborator:**

Florey Institute of Neuroscience and Mental Health, Melbourne, Australia/Professor Andrew Gundlach

**References:**

1.Bystritsky, A., et al. “Current Diagnosis and Treatment of Anxiety Disorders.”*Pharmacy & Therapeutics*, vol. 38, 2013, pp. 30-57

2. Ma, S., et al. “Relaxin-3 in GABA Projection Neurons of Nucleus Incertus Suggests Widespread Influence on Forebrain Circuits via G-Protein-Coupled Receptor-135 in the Rat.”*Neuroscience*, vol. 144, no. 1, 2007, pp. 165–90

3. Zhang, Cary, et al. “Central Relaxin-3 Receptor (RXFP3) Activation Reduces Elevated, but Not Basal, Anxiety-like Behaviour in C57BL/6J Mice.”*Behavioural Brain Research*, vol. 292, 2015, pp. 125-32