Functional roles of presynaptic opioid receptors

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Project description:

In the nervous system, GPCRs are expressed both on cell bodies of neurons (postsynaptically) as well as on nerve terminals and axons (presynaptically). Virtually all central mammalian nerve terminals express at least one GPCR where they function to control neurotransmitter release.

The vast majority of studies in GPCRs have been on postsynaptic receptors, yet presynaptic GPCRs play key physiological roles in neuronal transmission: affecting, for example, cognition, learning, stress responses, arousal, as well as being implicated in the aetiology of various disease states (e.g. Parkinson's disease, schizophrenia, addiction, depression, anxiety) and as sites of drug action (e.g. opioids). This project will focus on opioid receptors, a subtype of GPCR that are expressed both presynaptically and postsynaptically where they modulate a range of functions such as pain, mood and addiction.

Although presynaptic and postsynaptic GPCRs are the same receptor protein, they signal differently, and are regulated differently. We, and others, have shown that presynaptic opioid receptors evade receptor desensitization that occurs rapidly at postsynaptic receptors and that presynaptic opioid receptors are highly mobile and laterally diffuse along the axon and nerve terminal before signalling, whereas postsynaptic receptors are static in the cell membrane (Lowe JD & Bailey CP (2015) Br J Pharmacol 172:469-81; Jullie D et al (2020) Neuron 105:663-77).

In this innovative collaborative project the fundamental differences between presynaptic and postsynaptic opioid receptors will be investigated at the receptor, cellular and whole-animal level: how do they signal, how are they regulated, and what behavioural effects do they cause?

The student will utilise a range of complementary techniques: neuronal cell cultures, cell-based signalling assays, mathematical modelling of receptor signalling, rodent brain slice electrophysiology, whole animal rodent behaviour and viral-based in vivo gene transfer.