Structure and function of the $GABA_B$ receptor upon the binding and activation by analgesic peptides.

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Chronic pain affects more than 30% of people worldwide, producing a considerable mental, physical, and financial burden. As of 2018, 3.4 million Australians suffer from chronic pain conditions, contributing to an estimated financial cost of $139 billion. Unfortunately for those suffering from chronic pain, current therapeutic options are limited and associated with numerous side effects. For example, opiates, whilst effective at providing analgesia, are associated with side effects such as respiratory instability, sedation, dependence, and addiction. Given this, there is a strong need for the development of novel analgesics that provide effective pain relief with limited side-effects.

Conotoxins, are a group of peptides derived from the venom of marine cone snails (genus *Conus*) that are promising drug scaffolds due to their small size, target specificity, and structural stability. α-conotoxins such as Vc1.1, RgIA and PeIA are of particular interest due to their demonstrated analgesic activity in animal models of pain. The nociceptive activity of these conotoxins has been linked to their modulation of N-type voltage gated calcium channels and g-protein coupled inwardly rectifying potassium channels through activation of the $GABA_B$ Receptor. Activation of $GABA_B$ receptors has been shown to inhibit pain signalling in the peripheral and central nervous system, providing a promising target for the development of new analgesic drugs.

Whilst it is known that these α-conotoxins act through the $GABA_B$ receptor, the specific mechanisms that surround their activity requires further study. For example, the activity of Vc1.1 is maintained despite neutralisation of the orthosteric $GABA_B$ receptor binding site, indicating that it acts through an allosteric mechanism, however no structures have been determined to date. Furthermore, the precise mechanism of conotoxin action on the $GABA_B$ receptor is not yet known and further investigation is required. The use of sophisticated structural and functional techniques such as cryo-EM and patch-clamp electrophysiology will allow for further exploration of these questions and provide key insights into the activity of conotoxins.