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 the global population, imposing substantial mental, physical, and financial burdens[1]. Current therapeutic options remain limited and are often associated with significant side effects, highlighting the urgent need for novel analgesics that provide effective pain relief with minimal adverse effects.

Conotoxins are a diverse family of peptides derived from the venom of marine cone snails (genus *Conus*). They represent promising drug scaffolds due to their small size, high target specificity, and structural stability[2]. Among them, α-conotoxins, small peptides consisting of10-19 amino acids and two disulfide bonds, are known antagonists of nicotinic acetylcholine receptors (nAChR). Interestingly, several α-conotoxins, including Vc1.1, RgIA, and PeIA produce antinociceptive effects in animal models of chronic and neuropathic pain through activation of the γ-aminobutyric acid type B receptor ($GABA_BR$). $GABA_BR$ activation inhibits high voltage-activated calcium channels and activates G-protein-coupled inwardly rectifying potassium (GIRK) channels, leading to reduced neuronal excitability and attenuation of pain transmission[3].

Although a subset of a-conotoxins are known to act via the $GABA_B$ receptor, the precise mechanisms underlying their activity remain incompletely understood. Notably, the analgesic peptide Vc1.1 retains its activity even when the $GABA_BR$ orthosteric site is neutralized, suggesting an allosteric mode of action. However, no structural data have yet confirmed this mechanism[4]. Further studies are therefore needed to elucidate how these peptides modulate $GABA_BR$ function and downstream cellular signalling.

Here, we present findings on the effects of various $GABA_BR$ agonists including analgesic a-conotoxins on $GABA_BR$-mediated modulation of adenylyl cyclase and intracellular cAMP levels. We also outline the initial framework for structural characterization of the $GABA_BR$ in complex with a-conotoxins, providing a foundation for understanding their mechanism of receptor activation.

References

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