

P012 Vasopressin/oxytocin receptors... and love: towards rational design of a central non peptide agonist.

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Neuropeptide hormones arginine-vasopressin (AVP) and oxytocin (OT) have recently been described to play a crucial role in a broad range of attachment behaviours including social interactions, pair bonding, sexual behaviours or maternal care, all important for species survival. This mainly involves two of their four receptors, namely the V_{1A} and OT receptors, which are coupled to G proteins. Designing specific and bioavailable agonists to explore these functions *in vivo* remains a challenging task. Therefore, we developed a rational approach based on the docking of a series of non peptide, selective or non selective antagonists into the models of V_{1A} , V_2 and OT receptors. Their binding mode was compared to the AVP and OT binding one. We then designed and synthesised cleaved and hybrid analogues to investigate the switch in selectivity from one subtype to another and the switch in efficacy from antagonism to agonism. Results indicate that the affinity, specificity and efficacy molecular discriminants are very subtle both on receptors and on their ligands despite the high homology of receptor subtypes and the high similarity of their ligands.