Pharmacological exploration of peptide ligands with short residence-time at the oxytocin receptor

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Background: The neuropeptide oxytocin (OT) is implicated in the regulation of human social behaviour. This has led to broad interest in developing OT as a treatment in neuropsychiatric disorders characterized by impaired social function, such as autism spectrum disorder (ASD) and schizophrenia. Preliminary studies in humans (ASD/schizophrenic) using single-dose intranasal OT have shown promising, if transient, improvements in measures of social impairment. Chronic OT administration, however, produces negligible prosocial effects, associated with oxytocin receptor (OTR) desensitization and a concomitant reduction in receptor expression across the brain. This raises questions about the viability of OT therapeutics in disorders requiring life-long treatment regimes. Recently, the kinetics of agonist-receptor binding have been shown to influence receptor desensitization processes. Prolonged residence-time (defined as the $T_{1/2}$ of the drug-target complex) is correlated with rapid β -arrestin-mediated internalization of receptors across multiple neurotransmitter systems. Developing OTR ligands with short residence-time could therefore be an attractive strategy to reduce target internalization and extend therapeutic efficacy. With this in mind we sought to determine kinetic parameters for OT-OTR binding, and whether modifications to the OT peptide could produce molecules with fast-binding kinetics.

Methods: Affinity at the OTR was determined for OT and a series of C-terminally truncated OT-peptides using classical saturation & competition radioligand binding assays with [Tyrosyl-3,5- ^3H]-OT as the competing ligand. K_{on} , K_{off} and residence-time parameters were then determined for each peptide through competitive dissociation-association kinetics assays. Signalling potency and efficacy (EC_{50} , E_{max}) at the OTR was assessed using a cell-based homogenous-time resolved fluorescence assay.

Results: OT displayed high affinity (K_d 10 nM), potency (EC_{50} 35 nM) and prolonged residence-time (200 min) at the OTR. Truncation of the OT molecule produced peptides with attenuated residence-time (15-90 min) that retained affinity (K_d 50 -150 nM) and potency (EC_{50} 100-200 nM) in the nanomolar range, with partial agonist profiles (E_{max} 50 -70% of OT response) at the OTR.

Conclusions: Modified peptides derived from OT retained high affinity, potency and efficacy at the OTR with diminished residence-time. This property may extend therapeutic efficacy in chronic dosing regimes, thus further investigation of these molecules as therapeutics for social impairment is warranted.