

**P028** Elucidating direct binding contacts between vasopressin and the V<sub>1a</sub> vasopressin receptor

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The V<sub>1a</sub> vasopressin receptor (V<sub>1a</sub>R) is a G-protein-coupled receptor (GPCR) belonging to the rhodopsin-like, Family A, GPCRs. V<sub>1a</sub>R is activated by the neurohypophysial peptide hormone [arginine<sup>8</sup>]vasopressin (AVP) to generate a wide range of physiological responses. Elucidating the specific residues that provide ligand binding epitopes is of fundamental importance to understanding the mechanisms of activation of these receptors. In addition, identifying any epitope differences existing between receptor subtypes will aid rational drug design.

Site-directed mutagenesis of certain residues to alanine has previously identified several key residues of V<sub>1a</sub>R which are functionally important for agonist binding and signalling. This study describes modifications to both the ligand (AVP) and to the V<sub>1a</sub>R which define important interactions within the agonist binding site. Employing constructs incorporating reciprocal double mutations between the receptor and the ligand has enabled us to identify key epitopes in the receptor which make direct contact with the natural agonist AVP. A series of further mutations to these key residues showed the structural requirements at these key loci and explained the functional basis for the sequence conservation observed for V<sub>1a</sub>Rs from a range of species.

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