Relaxin family peptide

Overview: Relaxin family peptide receptors (RXFP, nomenclature as approved by the NC-IUPHAR committee on relaxin family peptide receptors, Bathgate *et al.* 2006) may be divided into two groups RXFP1/2 and RXFP3/4. Endogenous agonists at these receptors are a number of heterodimeric peptide hormones analogous to insulin: H1 relaxin [ENSG00000107018], H2 relaxin [ENSG00000107014], H3 relaxin [also known as INSL7, ENSG00000171136], insulin-like peptide (INSL) 3 [OTTHUMG00000070952*] and INSL5 [ENSG00000172410].

Species homologues of relaxin have distinct pharmacology – H2 relaxin interacts with RXFP1 and RXFP2, mouse and rat relaxin selectively bind to and activate RXFP1 (Scott *et al.*, 2005a) and porcine relaxin may have a higher efficacy than H2 relaxin (Halls *et al.*, 2005). H3 relaxin has differential affinity for RXFP2 receptors between species; mouse and rat RXFP2 have a higher affinity for H3 relaxin (Scott *et al.*, 2005b). At least two binding sites have been identified on the RXFP1 and RXFP2 receptors: a high-affinity site in the leucine-rich repeat region of the ectodomain and a somewhat lower-affinity site located in the surface loops of the transmembrane (Sudo *et al.*, 2003; Halls *et al.*, 2005). The unique *N*-terminal LDLa module of RXFP1 and RXFP2 is essential for receptor signalling (Scott *et al.*, 2006).

Nomenclature	RXFP1	RXFP2
Other names	Relaxin receptor, LGR7, leucine-rich repeat-containing G protein-coupled receptor 7, RX1	INSL3 receptor, LGR8, leucine-rich repeat-containing G protein-coupled receptor 8, GREAT, RX2
Ensembl ID	ENSG00000171509	ENSG00000133105
Principal transduction	G_s, $G_{\alpha oB}$, $G_{\alpha i3}$ (Hsu *et al.*, 2002; Halls *et al.*, 2006; 2009a)	G_s, $G_{\alpha oB}$ (Kumagai *et al.*, 2002; Halls *et al.*, 2006)
Rank order of potency	H2 relaxin > H3 relaxin >> INSL3 (Sudo *et al.*, 2003)	INSL3 > H2 relaxin >> H3 relaxin (Kumagai *et al.*, 2002; Sudo *et al.*, 2003)
Antagonists	LGR7-truncate (Scott *et al.*, 2006)	INSL3 B-chain analogue (Del Borgo *et al.*, 2006), (des 1-8) A-chain INSL3 analogue (Bullesbach and Schwabe, 2005)
Probes	[^{33}P]-H2 relaxin (0.2 nM, Sudo *et al.*, 2003), europium-labelled H2 relaxin (1 nM; Hossain *et al.*, 2009)	[^{33}P]-H2 relaxin (1.06 nM; Sudo *et al.*, 2003), [^{125}I]-INSL3 (0.1 nM; Muda *et al.*, 2005), europium-labelled INSL3 (0.9 nM; Shabanpoor *et al.*, 2008)

Mutations in *INSL3* and *LGR8* (RXFP2) have been reported in populations of patients with cryptorchidism (Ferlin *et al.*, 2003). Numerous splice variants of the human RXFP1 and RXFP2 receptors have been identified, none of which bind relaxin family peptides (Muda *et al.*, 2005). Splice variants of RXFP1 encoding the *N*-terminal LDLa module act as antagonists of RXFP1 signalling (Scott *et al.*, 2005b; 2006). cAMP elevation appears to be the major signalling pathway for RXFP1 and RXFP2 (Hsu *et al.*, 2000; 2002), but RXFP1 also activates MAP kinases, nitric oxide signalling and interacts with tyrosine kinases and glucocorticoid receptors (Halls *et al.*, 2007). RXFP1 signalling involves lipid rafts, residues in the C-terminus of the receptor and activation of phosphatidylinositol-3-kinase (Halls *et al.*, 2009a). The pattern of cAMP signalling observed is highly dependent on the cell type in which RXFP1 is expressed (Halls *et al.*, 2009b).

Nomenclature	RXFP3	RXFP4
Other names	Relaxin 3 receptor, GPCR135, somatostatin and angiotensin-like peptide receptor SALPR, RX3	INSL5 receptor, GPCR142, GPR100, relaxin 3 receptor 2, RX4
Ensembl ID	ENSG00000182631	ENSG00000173080
Principal transduction	$G_{i/o}$ (Matsumoto *et al.*, 2000); van der Westhuizen *et al.*, 2007)	$G_{i/o}$ (Liu *et al.*, 2003b)
Rank order of potency	H3 relaxin > H3 relaxin B chain (Liu *et al.*, 2003a)	INSL5 = H3 relaxin > H3 relaxin B chain (Liu *et al.*, 2003b; 2005a)
Antagonists	INSL5 (Liu *et al.*, 2005a), R3(BΔ23-27)R/I5 chimeric peptide (Kuei *et al.*, 2007)	R3(BΔ23-27)R/I5 chimeric peptide (Kuei *et al.*, 2007)
Probes	[^{125}I]-H3 relaxin (0.3 nM; Liu *et al.*, 2003a), [^{125}I]-H3-B/INSL5 A chimera (0.5 nM; Liu *et al.*, 2005b)	[^{125}I]-H3 relaxin (0.2 nM; Liu *et al.*, 2003b), [^{125}I]-H3-B/INSL5 A chimera (1.2 nM; Liu *et al.*, 2005b)

H3 relaxin acts as an agonist at both RXFP3 and RXFP4 whereas INSL5 is an agonist at RXFP4 and an antagonist at RXFP3. Unlike RXFP1 and RXFP2 both RXFP3 and RXFP4 are encoded by a single exon and therefore no splice variants exist. The rat RXFP3 sequence has two potential start codons that encode RXFP3L and RXFP3S with the longer variant having an additional 7 amino-acids at the *N*-terminus. It is not known which variant is expressed. Rat and dog RXFP4 sequences are pseudogenes (Wilkinson *et al.*, 2005). Recent studies suggest that H2 relaxin can interact with RXFP3 at a binding site distinct from that identified by H3 relaxin or analogues, and that this interaction activates pathways distinct from those activated by H3 relaxin (Summers *et al.*, 2009)

Abbreviations: H2 relaxin, human gene 2 relaxin; **H3 relaxin**, human gene 3 relaxin; **INSL3**, insulin-like peptide 3; **INSL5**, insulin-like peptide 5

Further Reading

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