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Review

Membrane receptors: Structure and function of the relaxin family peptide receptors

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ABSTRACT

The receptors for members of the relaxin peptide family have only recently been discovered and are G-protein-coupled receptors (GPCRs). Relaxin and insulin-like peptide 3 (INSL3) interact with the leucine-rich-repeat-containing GPCRs (LGRs) LGR7 and LGR8, respectively. These receptors show closest similarity to the glycoprotein hormone receptors and contain large ectodomains with 10 leucine-rich repeats (LRRs) but are unique members of the LGR family (class C) as they have an LDL class A (LDLa) module at their N-terminus. In contrast, relaxin-3 and INSL5 interact with another class of type I GPCRs which lack a large ectodomain, the peptide receptors GPCR135 and GPCR142, respectively. These receptors are now classified as relaxin family peptide (RXFP) receptors, RXFP1 (LGR7), RXFP2 (LGR8), RXFP3 (GPCR135) and RXFP4 (GPCR142). This review outlines the identification of the peptides and receptors, their expression profiles and physiological roles and the functional interactions of the peptides with their unique receptors.

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1. The relaxin peptide family

Relaxin was first discovered in 1926 when injection of serum from pregnant guinea pigs or rabbits caused relaxation of the interpubic ligament in virgin guinea pigs (Hisaw, 1926). Determination of the structure of the active hormone awaited development of reliable techniques to isolate and purify the peptide. Consequently, between the 1970s and 1990s, the primary sequence of relaxin was determined for the pig (Schwabe et al., 1976), rat (John et al., 1981), mouse (Evans et al., 1993), human (Hudson et al., 1984) and over 20 other species (Bryant-Greenwood and Schwabe, 1994; Bathgate et al., 2002b). Relaxin has the classic B–C–A structure of insulin peptides and belongs to a family of peptide hormones, the relaxin peptide family which is believed to have evolved from insulin early in the evolution of vertebrates (Bathgate et al., 2006a). This peptide family in humans encompasses relaxin-1 (Hudson et al., 1983), relaxin-2 (Hudson et al., 1984) and relaxin-3 (Bathgate et al., 2002a) plus insulin-like (INSL) peptide 3 (Adham et al., 1993) (also known as Leydig cell insulin-like peptide or relaxin-like factor), INSL4 (Chassin et al., 1995) (also known as early placenta insulin-like peptide), INSL5 (Conklin et al., 1999) (also known as relaxin–insulin-like factor 2) and INSL6 (Lok et al., 2000) (also known as relaxin–insulin-like factor 1) (Fig. 1).

The three relaxin peptides, relaxin-1, -2 and -3 are named due to the presence of the well characterized relaxin binding cassette (RXXXRXXI/V) in the peptide B-chain. The *RLN3* gene was discovered in 2002 and encodes a highly conserved neuropeptide which is the ancestral peptide of the relaxin family (Hsu, 2003; Wilkinson et al., 2005a). Humans and other higher primates possess the *RLN1*-encoded relaxin-1 peptide and the *RLN2*-encoded relaxin-2 peptide. The human *RLN1* gene arose as a result of an ancestral duplication of the human *RLN2* gene and human *RLN2* gene is the orthologue of the *RLN1* gene found in other mammalian species (Evans et al., 1994; Wilkinson et al., 2005b). Hence human relaxin-2 (H2 relaxin) is the equivalent of the relaxin peptide identified by Hisaw and produced by the corpus luteum and/or placenta during pregnancy in mammals. H2 relaxin in humans and relaxin-1 in other species is simply referred to as relaxin.

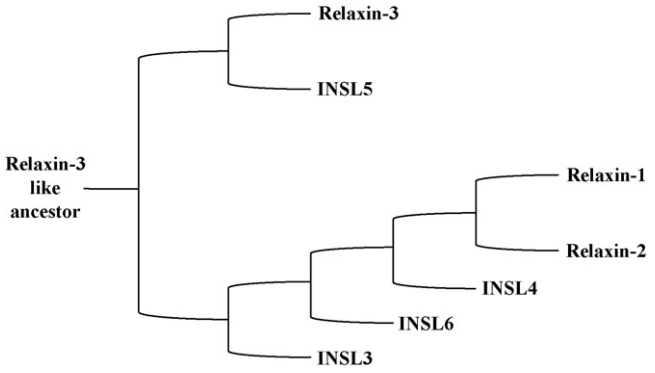

Fig. 1. Simplified phylogenetic tree of the relaxin peptide family.

1.1. Structure of the relaxin family peptides

All relaxin family peptides are synthesized as a pro-hormone composed of a signal sequence and a B–C–A domain. The signal peptide aids the secretion of the pro-hormone while the interconnecting C-chain facilitates the folding of the protein and the formation of the three disulphide bridges. The cleavage of the C-peptide *in vivo* to produce a mature peptide heterodimer of A- and B-chains linked by two interchain and one intrachain disulphide bond in the A-chain has only been proven for relaxin (Marriott et al., 1992), relaxin-3 (Liu et al., 2003b) and INSL3 (Bullesbach and Schwabe, 2002). However recombinant or synthetic peptides based on the heterodimeric structure have been produced for all the peptides and the crystal structure of H2 relaxin (Eigenbrot et al., 1991) and solution NMR structures of human relaxin-3 (H3 relaxin) (Rosengren et al., 2006a), INSL3 (Rosengren et al., 2006b) and INSL5 (Haugaard-Jonsson et al., 2009) have been solved (Fig. 2).

1.2. Relaxin

1.2.1. Effects on reproductive organs

Relaxin has traditionally been viewed as a hormone of pregnancy and parturition. As discussed above it was discovered in the early part of the last century as the factor that promoted pelvic girdle remodeling at delivery in mammals (Hisaw, 1926). Later it was also shown to inhibit spontaneous myometrial contractions and maintain uterine quiescence during pregnancy (Krantz et al., 1950). Subsequent studies have clearly shown relaxin, produced by the corpus luteum and/or placenta, is essential for normal pregnancy and parturition in many species. In the relaxin immunoneutralized rat (Guico-Lamm and Sherwood, 1988) and the relaxin knock out (KO) mouse (Zhao et al., 1999) parturition was difficult and

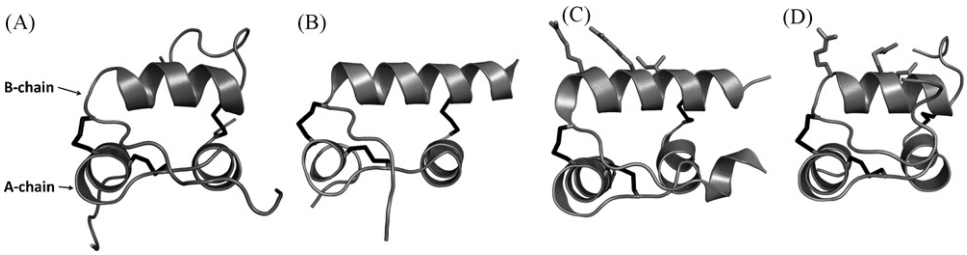

Fig. 2. Solved structures of: (A) INSL3 (Rosengren et al., 2006b). (B) INSL5 (Haugaard-Jonsson et al., 2009). (C) H2 relaxin (Eigenbrot et al., 1991) and (D) H3 relaxin (Rosengren et al., 2006a). This image shows that the relaxin peptides share a similar core structure. All of the relaxin family peptides exhibit a two-chain structure which is stabilised by a single intra-chain and two inter-chain disulphide bonds (in black). H2 and H3 relaxin display the relaxin-binding motif (Arg-X–X–X-Arg-X–X-Ile/Val), which is found on one face of the amphipathic B-chain helix facing into the solvent. INSL3 and INSL5 are not classified as being relaxin peptides as they lack this motif.