Sex-Steroid Regulation of Relaxin Receptor Isoforms (RXFP1 & RXFP2) Expression in the Patellar Tendon and Lateral Collateral Ligament of Female WKY Rats

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Abstract

The incidence of non-contact knee injury was found higher in female than in male and is related to the phases of the menstrual cycle. This raised the possibility that female sex-steroids are involved in the mechanism underlying this injury via affecting the expression of the receptors for relaxin, a peptide hormone known to modulate ligament laxity. Therefore, this study aims to investigate the effect of sex-steroids on relaxin receptor isoforms (RXFP1 & RXFP2) expression in the ligaments and tendons of the knee. Methods: Ovariectomized adult female WKY rats were treated with different doses of estrogen (0.2, 2, 20 μg/kg), progesterone (4mg) and testosterone (125 & 250;g/kg) for three consecutive days. At the end of the treatment, the animals were sacrificed and the patellar tendon and lateral collateral ligament were harvested for mRNA and protein expression analyses by Real Time PCR and Western blotting respectively. Results: RXFP1, the main isoform expressed in these knee structures and RXFP2 showed a dose-dependent increase in expression with estrogen. Progesterone treatment resulted in a decrease in expression of both relaxin receptor isoforms. Discussion: Progesterone and high dose estrogen up-regulate while testosterone down-regulates RXFP1 and RXFP2 expression in the patellar tendon and lateral collateral ligament of rat's knee. Conclusion: Relaxin receptor isoforms expression pattern could provide the basis for the reported increase in knee laxity while down-regulation of these receptor isoforms by testosterone could explain low incidence of non-contact knee injury in male.

Key words: RXFP1, RXFP2, sex-steroids, patellar tendon, collateral ligaments.

Introduction

Relaxin which consist of relaxin-1, -2 and -3 and insulin-like peptides (INSL3, 4, 5 and 6) [1] is a polypeptide hormone that possesses structural similarity to insulin and is primarily synthesized by the corpus luteum and placenta [2]. Relaxin binds to and activates G-protein-coupled receptors (GPCRs): RXFP1(LGR7) and RXFP2(LGR8) [3]. Human relaxins H1 and H2 activate both RXFP1 and RXFP2 [4], while rat relaxin1 binds weakly to RXFP2 [5]. Relaxin H3 binds selectively to RXFP1 as well as RXFP3 (GPCR135) and RXFP4 (GPCR142) [6]. RXFP1 and RXFP2 are the two main relaxin receptor isoforms [7].

Relaxin activity has been reported in both pregnant and non-pregnant female primates and non-primate vertebrates [8, 9]. In primates, ovarian relaxin is not required for successful term pregnancy.