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RELAXIN: A MULTI-FUNCTIONAL HORMONE

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ABSTRACT:
Relaxin is a polypeptide hormone produced in the human female by the corpus luteum of pregnancy and the decidua. It's most well-documented effects are on the menstrual cycle and during pregnancy. It is a key hormone which plays a major role during pregnancy, relaxing muscles, tendons, ligaments, and joints so that the body can handle the effects of a growing fetus. Although relaxin plays a major role during pregnancy, there are many other uses of relaxin. Relaxin enhances nitric oxide, prostacyclin and endothelium-derived hyperpolarization (EDH)-type-mediated relaxation in various vascular beds. These effects of relaxin on the systemic vasculature, coupled with its cardiac actions, reduce pulmonary capillary wedge pressure and pulmonary artery pressure. This results in an overall decrease in systemic and pulmonary vascular resistance in heart failure patients. The anti-fibrotic actions of relaxin are well established, a desirable property in the context of diabetes. Further, relaxin ameliorates diabetic wound healing, with accelerated angiogenesis and vasculogenesis. Relaxin-mediated stimulation of vascular endothelial growth factor (VEGF) and stromal cell-derived factor 1-α, as well as regulation of metalloproteinase expression, ameliorates cardiovascular fibrosis. Recent studies suggested that relaxin plays a beneficial role in treating cardiac problems, musculoskeletal problems and acts as anti- fibrotic agent, anti-inflammatory agent.

Keywords: relaxin, cardiac effects, anti-inflammatory, anti- fibrotic, relaxin treatment, serelaxin.

INTRODUCTION:

Relaxin is a peptide hormone of about 6000 Da belonging to the insulin family. Relaxin is a naturally occurring human peptide initially identified as a reproductive hormone. Like insulin, relaxin is composed by two disulfide-linked chains, termed the A and B chains, the B chain bearing the receptor interaction site. Relaxin is produced primarily by the corpus luteum, in both pregnant and nonpregnant females. It attains the highest plasma levels during pregnancy. In this condition, relaxin is also produced by the decidua and placenta. An additional source of relaxin has recently been identified in the heart atria. More recently, relaxin has been shown to play a key role in the maternal hemodynamic and renal adjustments that accommodate pregnancy. An understanding of these physiologic effects has led to the evaluation of relaxin as a pharmacologic agent for the treatment of patients with acute heart failure [1]. Relaxin meets several criteria of an effective anti-fibrotic based on its specific ability to inhibit pro-fibrotic cytokine and/or growth factor-mediated, fibroblast proliferation, differentiation

and matrix production. Furthermore, relaxin augments matrix degradation through its ability to up-regulate the release and activation of various matrix-degrading matrix metalloproteinases and/or being able to down-regulate tissue inhibitor of metalloproteinase activity. Relaxin can also indirectly suppress fibrosis through its other well-known (anti-inflammatory, antioxidant, anti-hypertrophic, anti-apoptotic, angiogenic, wound healing and vasodilator) properties.[2]. The effects of relaxin include the production of nitric oxide, inhibition of endothelin, inhibition of angiotensin II, production of VEGF, and production of matrix metalloproteinases. These effects lead to systemic and renal vasodilation, increased arterial compliance, and other vascular changes. [3]. The pleiotropic hormone, relaxin, is emerging as a novel antifibrotic therapy. Relaxin has been shown to limit collagen production and reorganization, while stimulating increased collagen degradation. It not only prevents fibrogenesis, but also reduces established scarring.[4] Relaxin exerts its regulatory effect on the musculoskeletal and other systems through binding to its receptor in various tissues, mediated by different signaling pathways. Relaxin alters the properties of cartilage and tendon by activating collagenase. This hormone is also involved in bone remodeling and healing of injured ligaments and skeletal muscle. [5] The other known biologic properties of relaxin, including anti-inflammatory effects, extracellular matrix remodeling effects, and angiogenic and anti-ischemic effects, all may play a role in potential benefits of relaxin therapy.

COMPARISON:

S.No	Title	Type of study	Sample	Result	Conclusion
1	Relaxin and extracellular matrix remodelling: Mechanisms and signalling pathways. Molecular and Cellular Endocrinology		Cell culture studies.	Relaxin was shown to decrease pathological collagen production by inhibiting its synthesis and secretion from myofibroblasts derived from numerous organs. Relaxin is able to promote the expression and activity of matrix metalloproteinases (MMPs), and/or decrease the levels of their endogenous inhibitors.	Relaxin plays a critical role in the protection of organs from age-related fibrosis. Relaxin inhibits the infiltration of various immune cells into injured/damaged organs, which produce various pro-inflammatory and pro-fibrotic factors to initiate the wound healing response to injury. Relaxin decreases granule exocytosis and mast cell degranulation to reduce pro-inflammatory and allergic cytokines such as histamine, leukotrienes and serotonin.
2	Relaxin mitigates microvascular damage and inflammation following cardiac ischemia–reperfusion Basic Research in Cardiology (2019) 114:30		Male C57Bl/6 mice at 12–14 weeks of age were used. open-chest surgery was performed to occlude the left coronary artery for a designated period followed by release of the occlusion for reperfusion for varying periods. To determine in vivo dosage of relaxin, human recombinant	The ischemic region showing no-reflow was reduced while the percentage of lumen-opening capillaries was higher in relaxin treated hearts. Third, the protective effect of relaxin was associated with suppressed regional inflammatory responses and modestly mitigated LV remodelling. relaxin was protective against endothelial leakage evoked by hypoxia, oxidative stress or	Relaxin therapy attenuated myocardial microvascular damage, specifically MVO and MVL, following cardiac IR injury as well as cultured cell model. This protection is not associated with limitation of infarct size, but accompanied with suppressed regional inflammatory response. A potential mechanism responsible for this protection is partially through preservation of VE-cadherin and relaxin

			relaxin peptide, we conducted a pilot experiment testing effect of different dosages of relaxin on MVL.	inflammatory cytokines, effect that is independent of NO but associated with preservation of protein abundance of VE-cadherin and RXFP1.	receptor in endothelial cells, but is NO-independent. Our findings indicate the therapeutic potential of relaxin targeting on IR-induced microvascular damage, complementing to current clinical management of acute MI.
3	Relaxin reduces endothelium-derived vasoconstriction in hypertension: Revealing new therapeutic insights British pharmacological society.	Research study	Male Wistar Kyoto rats (WKY) and SHR were subcutaneously infused with either vehicle (20 mmol·L−1 sodium acetate) or relaxin (13.3 μg·kg−1 ·hr−1) using osmotic minipumps for 3 days.	short-term relaxin treatment augments endothelial vasodilator function in resistance-size vessels.Subcutaneous infusion of relaxin for 3 days improved endothelial vasodilator function in the mesenteric arteries.	Relaxin treatment reversed EDC in the vasculature by altering expression and/or activity of IP receptors. Relaxin reversed hypertension-induced endothelial dysfunction in the mesenteric arteries by increasing basal NOS activity and NO-mediated relaxation, without any changes in eNOS and GTPCH1. Relaxin clearly has region-dependent effects on the vasculature, although the overall therapeutic endpoint is a reduction in EDC by restoring endothelium-derived PGI2 vasodilator pathways.
4	Relaxin enhances bone regeneration with BMP-2-loaded hydroxyapatite microspheres. Journal of biomedical materials research	Research study.	Male Sprague Dawley rats of 3-months-old were taken under a 12 h/12 h light/dark cycle. Rats were allowed to acclimate to diet, water, and housing for 14 days before experiments were conducted	All amounts of relaxin (0.05, 0.1, and 0.25 μg) showed new bone bridging.	The combination of 0.05, 0.1, and 0.25 μg of relaxin with 0.5 μg of BMP-2, as well as 0.05 μg of relaxin with 0.25 μg of BMP-2, all produced percentage areas of new bone. In addition to the enhancement effect mediated by relaxin, it is possible that the increase in bone formation seen with the combined microspheres could be due to the increased release of BMP-2 and relaxin. Addition of relaxin can lower the BMP-2 dose required for an equivalent amount of bone regeneration. Relaxin has the ability to lower BMP-2 doses with its enhancement effect, especially seen in the combination of 0.5 μg of BMP-2 with 0.05 μg of relaxin.
5	Relaxin-2 Suppress Endometriosis by		Endometriotic stromal cells	mRNA expressions of collagen-I and PAI-1	The contractile forces of ESCs were suppressed

	Reducing Fibrosis, Scar Formation, and Inflammation Advanced Research in Endometriosis		(ESCs) purified from surgical specimens were used in in vitro experiments	were decreased to around 50–60% in RLX-2-treated group compared to the control ($p < 0.05$), while those of CTGF and α-SMA were not changed. IL-8 protein concentration in cultured supernatant was significantly lower in 24 h-RLX-2 treated group compared to that in the control group.	with RLX-2 treatment significantly. RLX-2 increased the production of cAMP and decreased the phosphorylation of p38MAPK in ESCs. RLX-2 suppress endometriosis related events by suppressing p38 MAPK via cAMP/PKA activation in ESC. RLX-2 decreased the size of endometriotic-like lesions. As a reason for diminishing the size of lesions with RLX-2 stimuli, the fibrotic component in stromal lesions was decreased.
6.	Engineered Relaxin as theragnostic nanomedicine to diagnose and ameliorate liver cirrhosis BASIC SCIENCE: Nanomedicine: Nanotechnology, Biology, and Medicine 17 (2019) 106– 118		We conjugated RLX to PEGylated superparamagnetic iron-oxide nanoparticles (RLX-SPIONs) and examined hepatic stellate cells (HSCs) specific binding/uptake	RLX and RLX-SPIONs significantly inhibited TGFβ-induced migration. RLX has effects on matrix metalloproteinases (MMPs) expression and hence regulates collagen remodelling. RLX-SPIONs exhibited improved therapeutic efficacy without adverse effects.	RLX has been implicated as potent anti-fibrotic therapy for kidney and cardiac cirrhosis. In the liver, RLX has shown to lead to the dilation of sinusoids and changes in the contractility of activated HSCs or myofibroblasts. RLX has shown to result in a decreased collagen deposition and synthesis, accompanied by reduced expression of TIMP1 and TIMP2. RLX interaction with RXFP1 receptors results in the activation of the anti-fibrotic transcription factor PPARγ through cAMP, PKA, p38-MAPK and PPARγ coactivator protein 1α .

Discussion:

Relaxin, which is an important hormone in pregnancy, is stimulated by human chorionic gonadotropin. Relaxin is produced primarily by the corpus luteum.

Relaxin has a broad range of biologic activities, some of which have been known for a long time. These latter ones include: (a) the induction of collagen remodeling and consequent softening of the tissues of the birth canal in view of delivery; (b) the inhibition of uterine contractile activity; (c) the stimulation of growth and differentiation of the mammary gland. In particular, it has been shown that relaxin: (a) regulates growth and differentiation of breast cancer cells in culture; (b) promotes dilation of blood vessels in several organs and tissues, including the uterus, the mammary gland, the lung and the heart; (c) has a chronotropic action on the heart; (d) inhibits the release of histamine by mast cells, thus being able to counteract experimental allergic asthma; (d) depresses aggregation of platelets and their release by megakaryocytes; (e) influences the secretion of hormones by the pituitary gland; and (f) contributes to the regulation of fluid balance.

Ng HH et al stated that relaxin decreases granule exocytosis and mast cell degranulation to produce pro-inflammatory and allergic cytokines. Relaxin also inhibits the endothelial adhesiveness to neutrophils and the infiltration of macrophages which are crutial for the recruitment and migration of

inflammatory cells. Relaxin also reduces the pro-fibrotic influence of cytokines or mediators such as TGF-β1, IL-6, monocyte chemoattractant protein-1 and tumor necrosis factor-α.

Gao XM et al concluded that relaxin therapy attenuated myocardial microvascular damage. This is possible through preservation of VE-cadherin and relaxin receptor in endothelial cells, bit is nitric oxide independent.

Leo CH et al mentioned that relaxin treatment reversed endothelial cell vasculature by altering expression and/or activity of IP receptors. Relaxin acts as novel therapeutic agents for the treatment of the vascular complications of hypertension and other vascular diseases that are associated with increased endothelium-derived vasoconstriction.

Although relaxin produces vasoprotective effects in mesenteric arteries and aorta, this has not translated into a direct effect on BP. However, this does not preclude marked changes in the circulation, such as systemic arterial resistance, global arterial compliance, or cardiac output. Relaxin treatment reduces arterial load (by decreasing systemic vascular resistance and increasing arterial compliance) while also increasing cardiac output, heart rate, and stroke volume in hypertensive rats, without any effect on mean arterial pressure.

Nagórniewicz B et al stated that RLX has been implicated as potent anti-fibrotic therapy for kidney and cardiac cirrhosis. In the liver, RLX has shown to lead to the dilation of sinusoids and changes in the contractility of activated HSCs or myofibroblasts. RLX has shown to result in a decreased collagen deposition and synthesis, accompanied by reduced expression of TIMP1 and TIMP2. Serelaxin, a recombinant form of human relaxin-2[H2-RLX] relieved dyspnea, showed improvement in clinical outcomes and reduced mortality in acute heart failure patients in PHASE 3 trial.

Yoshino O et al concluded that the contractile forces of ESCs were suppressed with RLX-2 treatment significantly. RLX-2 increased the production of cAMP and decreased the phosphorylation of p38MAPK in ESCs. RLX has shown to result in a decreased collagen deposition and synthesis, accompanied by reduced expression of TIMP1 and TIMP2.

RLX-2 inhibited fibrosis, scar formation, and inflammation in endometriosis. But it has not been able to examine the efficacy of RLX-2 on pre-existing fibrosis. RLX-2 is expected to use in various fibrous diseases.

CONCLUSION:

Relaxin has region-dependent vasoprotective actions in hypertension. Specifically, relaxin has distinct effects on endothelium-derived contracting factors and their associated vasoconstrictor pathways in mesenteric arteries and the aorta. Taken together, these observations reveal the potential of relaxin as a new therapeutic agent for vascular disorders that are associated with endothelium-derived vasoconstriction including hypertension. Relaxin has protective effects in a variety of tissues. Exogenous relaxin treatment rapidly enhances endothelium -dependent vasorelaxation and decreases myogenic reactivity in a variety of vascular beds. Relaxin has a broader range of biological actions including anti -oxidant effects, suggesting it acts as a vasoprotective molecule limiting the damage inflicted by disease. Thus, relaxin is clearly differentiated from other ‘vasodilator’ agents and has the potential to be used as a therapeutic in cardiovascular diseases either alone or in combination with standard therapy.

RLX mediates its anti-fibrotic actions on TGF-β1 signal transduction and its interaction with the myofibroblast NLRP3 inflammasome. In summary, these findings highlight the therapeutic relevance of targeting the myofibroblast NLRP3 inflammasome as a means of treating the fibrosis that is a key cause of tissue dysfunction and failure. Hence relaxin can act as a potent therapeutic agent in the treatment of various diseases.

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