CHAPTER 6

The Vascular Actions of Relaxin

Arundhathi Jeyabalan, Sanjeev G. Shroff, Jaqueline Novak and Kirk P. Conrad*

Abstract

Relaxin is emerging as a hormone with important vascular actions. Much of our recently gained knowledge of relaxin in this context has stemmed from investigations of maternal vascular adaptations to pregnancy in which the hormone is turning out to be an important mediator. This chapter is separated into three parts. In Part 1, we discuss relaxin in the setting of normal vascular function and focus on systemic hemodynamics and arterial mechanical properties, renal and other peripheral circulations, angiogenesis, as well as the cellular mechanisms of the vasodilatory actions of relaxin. In this section, we also summarize the evidence for an arterial-derived relaxin ligand-receptor system. In Part 2, we present relaxin in the context of vascular dysfunction and the implications for relaxin as a therapeutic agent in renal and cardiac diseases, ischemia and reperfusion injury, pulmonary hypertension, vascular inflammation and preeclampsia. Finally, in Part 3, we highlight some of the controversies and unresolved issues, as well as suggest a general direction for future relaxin research that is urgently needed.

Introduction

The discovery that the vasculature may be another target of relaxin was made by Frederick L. Hisaw and colleagues. They reported that following administration of relaxin (Rlx) to castrated monkeys, there were profound morphological alterations in the endothelial cells of the endometrium consistent with hypertrophy and hyperplasia, as well as enlargement of arterioles and capillaries. The concept that relaxin alters vascular structure and function has been subsequently bolstered by numerous investigations, particularly in the last decade. Much of our recent understanding of relaxin as a vascular hormone has arisen from studies of maternal renal and cardiovascular adaptations to pregnancy in which relaxin is emerging as a pivotal player. The objective of this chapter is to review the vascular actions of relaxin.

Part 1. Contribution of Relaxin to Normal Vascular Function (Table 1)

Influence of Relaxin on Systemic Hemodynamics and Arterial Mechanical Properties

Definitions

Systemic arterial load is defined as the mechanical opposition to the flow of blood out of the left ventricle. There are 2 components. The first is the steady arterial load commonly known as systemic vascular resistance (SVR), which is calculated by the quotient of mean arterial pressure and cardiac output (CO) and results mainly from arteriolar properties. The second is pulsatile arterial
Table 1. Summary of the contribution of relaxin to normal vascular function

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| I. Systemic Hemodynamics and Arterial Mechanical Properties | - RLX administration increases cardiac output and arterial compliance, and reduces systemic vascular resistance and myogenic reactivity in rats.  
- Endogenous, circulating relaxin mediates the increased cardiac output and arterial compliance, and the reduced systemic vascular resistance and myogenic reactivity during mid-term pregnancy in rats. |
| II. Renal Circulation | - RLX administration reduces renal vascular resistance and increases renal plasma flow and glomerular filtration rate in rats and humans.  
- Endogenous, circulating relaxin mediates the reduced renal vascular resistance and increased renal plasma flow and glomerular filtration rate during pregnancy in rats.  
- Endogenous, circulating relaxin contributes to increased glomerular filtration rate during pregnancy in women. |
| III. Other Organ Circulations | - RLX administration increases blood flow in other organ circulations: coronary, uterus, mammary gland, liver, mesentery and mesocaecum. |
| IV. Angiogenesis | - RLX has been shown to be angiogenic in the endometrium, and in the setting of wound healing and myocardial infarction. |
| V. Local Vascular Relaxin Ligand-Receptor System | - Recent evidence indicates the local expression of relaxin ligand and receptor in arteries that increases arterial compliance and reduces myogenic reactivity. |

load, which becomes relevant because of the inherently pulsatile nature of the cardiac pump and is determined by vessel geometry and wall visco-elasticity, the branching of the vasculature that yields wave propagations and reflections and the mechanical attributes of blood. Together, the steady and pulsatile arterial loads constitute a comprehensive characterization of total hydraulic load in terms of arterial mechanical properties. Global arterial compliance (global AC) is one measure of pulsatile arterial load, which is derived from CO and the diastolic decay of the aortic pressure waveform or more simply from the ratio of the stroke volume and pulse pressure.

Systemic Hemodynamics and Arterial Mechanical Properties during Pregnancy

A fundamental cardiovascular adaptation to human pregnancy is the increase in global AC which reaches a peak by the end of the first or beginning of the second trimester just as SVR reaches a nadir. At least in theory, the increase in global AC is essential to the maintenance of cardiovascular homeostasis during pregnancy for several reasons: (i) by preventing an excessive fall in diastolic pressure which otherwise would decline to precariously low levels due to the large drop in SVR; (ii) by minimizing the pulsatile or oscillatory work (i.e., wasted energy) which otherwise would rise disproportionately to the increase in total work required of and expended by the heart during pregnancy; (iii) by contributing to arterial underfilling along with the reduction in SVR (albeit to a lesser degree than SVR), both of which abet renal sodium and water retention and plasma volume expansion during early pregnancy; and (iv) by preserving steady shear relative to steady shear stress at the blood-endothelial interface in the setting of the hyperdynamic circulation of pregnancy, thus favoring nitric oxide production by the endothelium over that of superoxide and other potentially damaging reactive oxygen species.

Influence of Relaxin Administration on Systemic Hemodynamics and Arterial Mechanical Properties in Nonpregnant Females and Males

Because relaxin mediates the maternal renal circulatory changes during pregnancy in rats, it was logical to consider whether the hormone might also underlie the broader cardiovascular ad-