Effects of Intraperitoneal Installation of Propranolol on Vascular Smooth Muscle Cell (VEGF) Expression in Rat Model of Surgically Induced Endometriosis

Thesis

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Epidemiology:

The exact prevalence of endometriosis in the population today is difficult to determine because it is asymptomatic or subclinical in the majority of cases. The prevalence has been estimated to be as low as 1% among asymptomatic women and as high as 60% in women with chronic pelvic pain ***(Abbas et al., 2012; Janssen et al., 2013)***.

In women with infertility, the prevalence ranges from 20-50% ***(Balasch et al., 1996)***. This may be due to the fact that endometriosis plays a causative role in infertility, but it also may be due to a diagnostic selection bias, as women with infertility typically undergo laparoscopy as part of their clinical evaluation ***(Sundheimer et al., 2014)***. Endometriosis is present in 71-87% of women with chronic pelvic pain ***(Ling, 1999)***.

Between the years 1965 and 1984, endometriosis increased from 10-19% as the primary indication for hysterectomy in the USA. Interestingly, this happened during a time in which a trend towards more conservative therapies as treatment modalities for endometriosis occurred ***(National Center for Health Statistics, 1987)***. This finding suggests a true increase in the incidence of the disease ***(Sundheimer et al., 2014)***.

Contents

List of Abbreviations

AAG : α1-acid glycoprotein

ASRM : Reproductive Medicine

bFGF : Basic fibroblast growth factor

DIE : Deep infiltrating endometriosis

ERK : Extracellular-signal-regulated kinase

ESHRE : The European Society of Human Reproduction and Embryology

flt : fms-lime tyrosine kinase

FSH : Follicle stimulating hormone

GnRH : Gonadotropin-releasing hormone

HRT : Hormone replacement therapy

ISA : Intrinsic sympathetic activity

KDR : Kinase domain receptor

LH : Luteinizing hormone

LNG-IUS : The levonorgestrel intrauterine system

MMPs : Metalloproteinases

NRP : Neuropilins

OCPs : Oral contraceptives

PlGF : Placenta growth factor

ROS : Reactive oxygen species

TNF-α : Tumor necrosis factor-α

VEGF : Vascular endothelial growth factor

VSMC : vascular smooth muscle cell

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Introduction

Endometriosis is an estrogen-dependent disease affecting 8% to 10% of females of reproductive age. It is diagnosed in 71% to 87% of females with chronic pelvic pain and in 30% of women with infertility ***(McLaren, 2000)***, it is defined as adherence and growth of the functional layer of the endometrium outside the uterine cavity.

In Endometriotic lesions, the development of new blood vessels from pre-existing ones is necessary to supply oxygen and essential nutrients ***(Fischer et al., 2011)***, a process that is coordinated by a sequence of humoral and cellular interactions ***(Starkey and Shahidullah, 2011).*** Vascular endothelial growth factor (VEGF) is of primary importance as a mediator of angiogenesis in endometriosis in addition to its potent endothelial cell-mitogen-, morphogen-, and vascular permeability-inducing activities ***(Vernon and Wilson, 1985; Machado et al., 2010).*** Furthermore, metalloproteinases (MMPs) influence the outcome of inflammatory reactions, angiogenesis, and tissue remodeling through regulation of extracellular matrix turnover ***(Bertrand et al., 2012; Demirel et al., 2014).***

VEGF is a secreted, hepatin-binding homodymetic glycoprotein of ~46 kD, with several protein variants

resulting from alternative splicing of VEGF mRNA ***(Houck et al., 1991; Charnock-Jones et al., 1993).*** VEGF binds to either one of two tyrosine kinase receptors, the fms-lime tyrosine kinase (flt) ***(de Vries et al., 1992)*** and the kinase domain receptor (KDR) ***(Terman et al., 1993)***. These receptors are found predominately on endothelial cells ***(Ferrara et al., 1992; Jakeman et al., 1992; Connolly et al., 1994)***, and activation leads not only to the expression of a number of preteolytic enzymes involved in the process of angiogenesis ***(Pepper et al., 1991; Unemor et al., 1992).***

An important mediator of angiogenesis is vascular endothelial growth factor (VEGF)[1]. VEGF is a secreted, heparin-binding homodymeric glycoprotein of ~46 kD, with several protein variants resulting from alternative splicing of VEGF mRNA ***(Houck et al., 1991; Charnock-Jones et al., 1993).*** VEGF binds to either one of two tyrosine kinase receptors, the fms-like tyrosine kinase (flt) ***(de Vries et al., 1992)*** and the kinase domain receptor (KDR) ***(Terman et al., 1993).*** These receptors are found predominately on endothelial cells ***(Ferrara, et al., 1992; Jakeman et al., 1992; Connolly et al., 1994),*** and activation leads not only to proliferation and increased vascular permeability but also to the expression of a number of proteolytic enzymes involved in the process of angiogenesis ***(Pepper et al., 1991; Unemor et al., 1992).***

Propranolol is a non-selective beta-blocker that demonstrates equal affinity for adrenoreceptors and therefore acts on multiple tissues, propranolol has been found to be potent and sale for treatment of hemangiomas by inhibition of angiogenesis ***(MacLaren et al., 1996).*** Beta-blockers also decrease the expression of VEGF, thus preventing angiogenesis ***(Pupo-Nogueira et al., 2007).***

Based on these data, the propranolol inhibits angiogenesis, which plays a critical role in the pathogenesis of endometriosis. Thus, the aim of this study will be to investigate whether propranolol has an inhibitory effect on the angiogenesis of endometriosis in an experimental rat model. For this aim, should evaluated VEGF, MMP2 and MMP9 immunoreactivity in endometriosis lesions.

Aim of the Study

To study the effects of intraperitoneal instillation of propranolol VEGF expression in rate model of surgical induced endometriosis.

Research hypothesis:

In rat model of surgically induced endometriuosis, intraperitoneal propronolol instillation may suppress the growth of endoemtrosis.

Research questionnaire:

In rat model for surgically induced enodmetriosis does intraperitoneal instillation suppress the growth of endometriosis.