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Peroxisome proliferator-activated receptor (PPAR) expression in cultured bovine endometrial cells and response to omega-3 fatty acid, growth hormone and agonist stimulation in relation to series 2 prostaglandin production

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Abstract

The peroxisome proliferator-activated receptors (PPARs) are a family of nuclear transcription factors thought to act as receptors for polyunsaturated fatty acids and to reduce production of series 2 prostaglandins (PG). The objectives of the current study were to characterize PPAR expression and the prostaglandin synthetic activity of cultured bovine endometrial cells in response to known PPAR ligands, as well as to key stimulators and inhibitors of series 2 prostaglandin secretion. PPARα and PPARδ, but not PPARγ, mRNAs are expressed in the BEND cell line regardless of treatment. Under resting conditions, PPARα mRNA levels increase in response to growth hormone ($P < 0.05$). In cells stimulated with PdBu, growth hormone depresses PPARα mRNA levels, regardless of whether cells also are treated with IFNτ. In contrast, PPARδ mRNA levels are increased by exposure to PdBu, eicosapentanoic acid and IFNτ, and these effects are additive. PPAR mRNA levels are not predictive of prostaglandin accumulation. Agonist activation of PPARα, PPARδ or PPARγ augments PdBu-induced

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increases in prostaglandin H synthase-2 mRNA and media accumulation of prostaglandins $F_{2\alpha}$ and E_2. Treatment with the PPARα/δ agonist carbaprostacyclin, but not the PPARα agonist Wy14643 or PPARγ agonist ciglitazone, completely reverses the IFNτ suppression of prostaglandin synthesis. In conclusion, PPARα and PPARδ function in the response of bovine endometrium to growth hormone and long chain omega-3 polyunsaturated fatty acids.

Keywords: Pregnancy; Female reproductive tract; Polyunsaturated fatty acid; Peroxisome proliferator-activated receptor; Prostaglandin

1. Introduction

The peroxisome proliferator-activated receptors (PPARs) are a family of nuclear receptors activated by selected long chain fatty acids, eicosanoids and peroxisome proliferators. There are three subtypes of PPAR (i.e., α, δ and γ) that upon ligand binding, heterodimerize with the retinoid receptor RXR and interact with specific PPAR response elements in the promoter region of target genes to affect transcription. Regulation of promoter function is complex, since there is tissue specific expression of the PPAR and RXR subtypes, competition for the RXR binding partner, and differences in binding affinity among the PPAR subtypes and among the RXR subtypes [1]. PPAR activation may be ligand dependent or independent, and there is also cross-talk with other nuclear receptors and their response elements, as well as several transcription factors [1,2]. The PPARs are best known for their roles in lipid metabolism, but they are also involved in development, nervous tissue, lung, kidney and cardiac functions, epidermal maturation and reproduction in several animal models [1,3].

A distinctive feature of ruminant endometrium is its role in control of the estrous cycle. If the female is not pregnant, at about day 16 postestrus the endometrial epithelial cells differentiate in response to oxytocin receptor stimulation and secrete large amounts of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) in a pulsatile manner [4]. This $PGF_{2\alpha}$ is delivered to the ovarian arterial blood from the uterine vein by a countercurrent mechanism, and causes luteolysis and subsequent return to estrus at about day 21. During pregnancy, the trophoblast of the elongating embryo produces interferon-tau (IFNτ), which suppresses oxytocin receptor upregulation and pulsatile $PGF_{2\alpha}$ secretion. Supplementation of dairy cow diets with long chain omega-3 polyunsaturated fatty acids (PUFA) such as those found in flax or fish oil improves reproductive performance, likely by decreasing uterine $PGF_{2\alpha}$ production and increasing embryo survival [5,6]. Our recent studies with a bovine cell line derived from endometrial epithelial cells showed that omega-3 long chain PUFA added to culture medium depress $PGF_{2\alpha}$ secretion [7], and others have found similar results using cultured human decidual cell lines [8]. The mechanism for this inhibition is not known, but long chain omega-3 PUFA are known to affect eicosanoid signaling in a variety of ways: they reduce the efficiency of the prostaglandin H synthase (also known as cyclooxygenase) enzymes which regulate prostanoid synthesis, increase eicosanoid catabolism and favor the production of less biologically active products, including the production of series 1 and 3 prostaglandins at the expense of series 2 prostaglandins [9,10]. There is evidence that