



## Review of Literature on the role of PGs in physiological functioning of granulosa cells

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**Abstract:** Prostaglandins are a group of 20-carbon fatty acids produced from arachidonic acid via the cyclooxygenase pathway in response to extrinsic stimuli (Smith 1989, 1992; Smith et al., 1991; Smith et al., 2011). Prostanoid biosynthesis (including classical prostaglandins PGD, PGE and PGF, as well as prostacyclins and thromboxanes) proceeds in three stages: (1) extrinsic stimuli-activated mobilization of esterified arachidonate from precursor lipids in the cell membrane through the action of lipases, (2) conversion of arachidonate to the prostaglandin endoperoxide (PGH<sub>2</sub>) mediated by PGH synthases, and (3) cell-specific isomerization or reduction of PGH<sub>2</sub> by specific synthases (isomerases) or reductases to the major biologically active prostanoids PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2</sub> $\alpha$ , prostacyclin (PGI<sub>2</sub>), or thromboxane A<sub>2</sub> (TXA<sub>2</sub>; Figure 1, modified from Smith, 1992; Smith et al., 2011). Prostaglandins are local hormones (i.e. autocooids; Smith 1989, 1992; Smith et al., 1991). Infused PGE and PGF derivatives fail to survive a single pass through the circulatory system. Their synthesis is not restricted to a central endocrine organ, but rather occurs in most organs, although not necessarily in all cell types. The plasma concentrations of these compounds, except in rare situations, are less than 10<sup>-9</sup>M, a concentration normally unable to elicit responses.

[Vivek Kumar Singh, Mukesh Kumar. **Review of Literature on the role of PGs in physiological functioning of granulosa cells.** *J Am Sci* 2024;20(12):261-264]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). <http://www.jofamericanscience.org>. 05 doi:[10.7537/marsjas201224.05](https://doi.org/10.7537/marsjas201224.05)

**Keywords:** Review of Literature; PGs; physiological functioning; granulosa cells

### Introduction:

Prostaglandins of the E series, primarily E<sub>2</sub> and E<sub>1</sub>, have the greatest activity in bone. Following discovery of their potent ability to stimulate bone resorption in vitro, clinical investigations have placed prostaglandins at sites of localized bone resorption associated with inflammatory or space occupying lesions in vivo. These studies have shown that prostaglandin production at such sites may be increased by cytokines such as interleukin-1 but the mechanisms by which prostaglandins stimulate bone resorption are not yet known.

Observation of periosteal bone formation in patients given, pharmacological doses of prostaglandin has led to investigation of its bone forming activity. Young, growing rats have increased metaphyseal bone formation and this is accompanied by increased periosteal and endocortical bone formation in older animals. In the mature animals there is a generalized activation of remodeling with increased formation in the remodeling cycle. This is also seen in oophorectomized rats and results in repletion of the lost bone in this model of osteoporosis. In animal models of localized disuse osteopenia, prostaglandins are found to be elevated at the site of bone loss and prostaglandin inhibitors at least partially protect against the exaggerated resorption that occurs. This is

also seen in models of orthodontic tooth movement, periodontitis and osteomyelitis.

Prostaglandin synthesis inhibitors have been shown to delay healing of bone and this has led to limitations on their use clinically in some situations. Exogenously administered prostaglandins have been found to enhanced periosteal callus formation, but healing is not uniformly enhanced.

Prostaglandins have also been associated with hypercalcemia in certain animal tumors that model human hypercalcemia of malignancy but are probably most important in this condition as mediators in the localized resorption of bone at tumor sites.

These in vivo studies have shown that prostaglandins are involved with increases in both bone formation and bone resorption. In vitro studies have shown that prostaglandins stimulate osteoblasts as well as osteoclastic bone resorption but understanding these effects under in vivo conditions will require further investigation.

### Review of Literature

Induction of labour (IOL) is one of the most common medical procedures used in obstetrics. It is estimated that currently in developed countries the induction of labour affects every 4th pregnant woman [1]. In developing countries, the prevalence of IOL differs significantly from centre to centre. Recently, new data

on the safety of this procedure as well as on the benefits of using it even in low-risk pregnancies at the end of 39 weeks of pregnancy are emerging [2]. This is likely to result in further expansion of the indications for IOL [3]. In addition, the worldwide availability of methods for monitoring foetal and maternal well-being and epidemiological data on the possibility of reducing maternal and foetal mortality and morbidity in certain pregnancy complications (i.e. intrauterine growth restriction, gestational diabetes mellitus, intrahepatic cholestasis of pregnancy, preeclampsia, prelabour rupture of membranes) is likely to result in an increased percentage of IOL in the future. This paper aims to provide the reader with information on the physiological role of prostaglandins in the parturition process and the availability of their synthetic analogues on the market, and to present the current knowledge on the differences between them. This is a narrative review. We based this paper on articles published in the Medline database in the last 10 years and information provided by drug manufacturers in summaries of product characteristics. The papers were subjectively chosen based on their substantive value (mainly systematic reviews, meta-analyses, and controlled randomized trials). No specific search strategy was used.

Prostaglandins (PGs) in the human organism are formed in the so-called arachidonic acid cascade. Arachidonic acid released from the cell membrane can be metabolized into intermediate products (PGG<sub>2</sub> and PGH<sub>2</sub>) by means of constitutional cyclooxygenase 1 (COX-1) or cyclooxygenase 2 (COX-2), the activity of which is regulated by growth factors and cytokines. Intermediate products are used to produce prostacyclins, thromboxanes, and prostaglandins, of which the most important ones involved in parturition physiology are PGE<sub>1</sub>, PGE<sub>2</sub>, and PGF<sub>2</sub> $\alpha$  [9]. Prostaglandins are produced in all compartments of the maternal reproductive system (decidua, muscles of uterus, and cervix) as well as in the foetal membranes. Each of these compartments has its own specific concentration profile. The concentration of prostaglandins increases in urine, amniotic fluid, and maternal plasma before the onset of uterine contraction, which proves that the increase is not the result of the onset of labour but one of its causes [12]. Prostaglandins can induce myometrial contractility, proteolysis of the extracellular matrix of the cervix (cervical ripening), and promote rupture of membranes [12]. Cyclooxygenase inhibitors are also used as tocolytic drugs (indomethacin). The administration of prostaglandins induces an abortion in the case of termination of pregnancy or missed abortion and promotes cervical ripening and the onset of delivery [12]. Three analogues of prostaglandins: PGE<sub>1</sub>

(misoprostol), PGE<sub>2</sub> (dinoprostone), and PGF<sub>2</sub> $\alpha$  (dinoprost), are used in obstetric practice, of which misoprostol and dinoprostone are most commonly used in the pre-induction of labour.

Similar differences are now emerging at the molecular level in the human dorsal root ganglion (DRG) [42; 43; 56] suggesting that sex differences in basic pain mechanisms may contribute to differential efficacy of pain therapeutics in men and women. We recently identified a sex difference in DRG neuron expression of a prostaglandin synthesizing enzyme, PTGDS, that led to differences in behavioral outcomes in response to prostaglandins and PTGDS inhibitors in male and female mice [55]. This finding prompted us to look more carefully at the clinical and preclinical research on prostaglandins and their receptors with the hypothesis that the very commonly used drugs that target this pathway may have differential efficacy in men versus women.

The four major prostaglandins, prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), prostaglandin D<sub>2</sub> (PGD<sub>2</sub>), prostacyclin (PGI<sub>2</sub>), and prostaglandin F<sub>2</sub> $\alpha$  (PGF<sub>2</sub> $\alpha$ ) act on G-protein coupled receptors to regulate intracellular signaling pathways [44]. PGE<sub>2</sub> acts on the E prostanoïd receptors EP<sub>1</sub>, EP<sub>2</sub>, EP<sub>3</sub>, and EP<sub>4</sub>. As G<sub>s</sub>-coupled receptors, EP<sub>2</sub> and EP<sub>4</sub> activate adenylyl cyclase to produce cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP); as a second messenger, cAMP phosphorylates protein kinase A (PKA), which in turn can phosphorylate intracellular target proteins [44]. EP<sub>3</sub> is a G<sub>i</sub>- and G<sub>12</sub>-coupled, lowering cAMP, increasing intracellular calcium and the activity of rho GTPases [44] and this receptor has been linked to anti-nociceptive actions of PGE<sub>2</sub> [31]. EP<sub>1</sub> is a G<sub>q</sub>-coupled receptor, whose activation causes phospholipase C to catalyze conversion of phosphatidylinositol biphosphate (PIP<sub>2</sub>) into inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG). All 4 EP receptor genes are expressed in mouse [69] and human [56] DRG neurons where their expression varies depending on the subtype of receptor and the type of sensory neuron. EP<sub>1</sub>, 2 and 4 receptors are known to sensitize ion channels like the TRPV1 receptor and voltage gated sodium channels that regulate the excitability of sensory neurons [10; 14]. Marine organisms have a great potential to produce a vast variety of bioactive molecules with high antibiotic, anti-proliferative, and anti-inflammatory activity [1]. The biodiversity hosted by the oceans is greater than in terrestrial environments [2] but nonetheless, marine bioresources are still underexplored, and many species await to be discovered.

The high probability to find new interesting bioactive molecules from marine organisms has fostered the effort of the scientific community to adopt new technologies and approaches to increase the success of

biodiscovery from marine resources, with a main focus on products with antibiotic, antitumor and anti-inflammatory activities. Of particular interest is the search for new anti-inflammatory compounds since inflammation processes are often related to the onset of chronic pathologies and tumors.

Indeed, inflammation processes represent a fundamental way to restore the original equilibrium of a cell or tissue whose physiology has been impaired by damaging stimuli [3]. At the same time, if inflammation is not blocked it can stimulate a cascade of events that eventually lead to serious diseases such as cancer and autoimmune disorders [4]. The inflammation-resolution process can have different features depending on the type of tissue and injurious stimulus [5], therefore, specific types of pro-resolution stimuli or drugs may be necessary [6]. Both the onset and the resolution of the inflammation are active processes that involve a complex interplay of different molecules [7] like chemokines, cell adhesion molecules, proteolytic enzymes, eicosanoids [8], reactive oxygen species (ROS), and reactive nitrogen species (RNS) [9,10]. Among these, eicosanoids deriving from oxidation of polyunsaturated fatty acids (PUFA) through cyclooxygenase (COX) and lipoxygenase (LOX) pathways play a pivotal role both in the onset and in the resolution of inflammation [9]. The main products of COX enzymes are prostaglandins (PGs), fatty acid derivatives with a molecular structure based on 20 carbon atoms that share a prostanoid acid skeleton.

Prostaglandin E2 was the first PGs to be identified in the early 1930s in human seminal plasma by Von Euler [11] and, independently, by Goldblatt [12] although the chemical structures were determined only 30 years later by Bergström, Samuelsson, and co-workers [13].

PGs action is mediated by the interaction with specific receptors present on the plasma membrane. These are transmembrane G-protein coupled receptors (GPCR), named as prostaglandin EP receptor (EP), prostaglandin F2 $\alpha$  receptor (FP), prostaglandin DP receptor (DP), and prostacyclin I2 receptor (IP) receptors, that are highly selective for PGE2, PGF2 $\alpha$ , PGD2, and PGI2, respectively [26]. The EP family comprises four isoforms (EP1-4) that play a relevant role in inflammation processes [27]. The downstream signaling of this receptor family is responsible for the pleiotropic ability of PGE2 to activate different processes, including cell proliferation, apoptosis, angiogenesis, inflammation, and immune surveillance in different cell types [24].

Most prostaglandins display a marked structure-activity specificity mainly determined by substitutions in the cyclopentanone ring and the degree of unsaturation of the side chains. They exert their

function once secreted into the extracellular medium, where they are rapidly metabolized by 15-hydroxyprostaglandin dehydrogenase (15-OH-PGDH). This enzyme selectively oxidizes the hydroxyl group at carbon 15 into a 15-keto derivative [28] accompanied by a substantial loss of biological activity.

Prostaglandins derive from the sequential actions of highly specific enzymes (Figure 1). Their synthesis is initiated by phospholipases A2 (PLA2), a family of enzymes that hydrolyze membrane phospholipids at the sn-2 position, liberating free fatty acid precursors, mainly ARA [15]. These enzymes represent a key step in the PG biosynthetic pathway, being regulated by Ca<sup>2+</sup> binding and phosphorylation by mitogen-activated protein kinase (MAPK) in response to different stimuli. Membrane-released ARA is then rapidly converted through the cyclization and inclusion of molecular oxygen in the precursor by the action of cyclooxygenase (COXs) enzymes into the unstable metabolite PGG2, which is subsequently reduced to PGH2 by the same enzyme [14]. Cyclooxygenases exist in a substrate-limiting environment; thus, liberation of fatty acids from esterified stores results in the prompt formation of the products. There are two major COX isoforms; COX-1 is constitutively active and present in most cells in the body; expression of the COX-2 isoform is inducible in many tissues by pro-inflammatory and mitogenic stimuli, such as cytokines [29]. The specific transformation of the first product PGH2 to other PGs and thromboxanes (TXs) by downstream enzymes is complexly orchestrated and is cell specific, since each cell tends to form mainly one of these compounds as the major product. For example, in brain and mast cells, PGH2 is converted to PGD2, whereas it is converted in PGF2 $\alpha$  in the uterus; from the same precursor, vascular endothelial cells produce PGI2 (prostacyclin) and platelets release thromboxane A2 (TXA2).

### Conclusion:

Prostaglandins (PGs) are lipid mediators belonging to the eicosanoid family. PGs were first discovered in mammals where they are key players in a great variety of physiological and pathological processes, for instance muscle and blood vessel tone regulation, inflammation, signaling, hemostasis, reproduction, and sleep-wake regulation. These molecules have successively been discovered in lower organisms, including marine invertebrates in which they play similar roles to those in mammals, being involved in the control of oogenesis and spermatogenesis, ion transport, and defense. Prostaglandins have also been found in some marine macroalgae of the genera *Gracilaria* and *Laminaria* and very recently the PGs pathway has been identified for the first time in

some species of marine microalgae. In this review we report on the occurrence of prostaglandins in the marine environment and discuss the anti-inflammatory role of these molecules.

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11/21/2024