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Review

Cyclooxygenase pathways

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This review compiles the current knowledge on the effects of prostanoids — arachidonic acid metabolites — on their own synthesis, activity and degradation. Interaction mechanisms between the receptors for the relevant compounds are presented, in particular with regard to the cooperation between a thromboxane A_2 and prostaglandin I_2 receptors. The questions of desensitization and internalization of receptors are discussed. The stages of the inflammatory response and tumor progression are analyzed against the background of the disruption of the synthesis of prostanoids. Special attention is given to the significance of 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 in the regulation of the synthesis of prostanoids and its role as an anti-inflammatory agent. Ultimately, therapeutic approaches as used in various treatments are discussed in the light of the available knowledge.

Key words: cyclooxygenase, prostaglandin, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2, receptor desensitization

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BIOSYNTHESIS AND BIOLOGICAL IMPORTANCE OF PROSTANOIDS

Prostanoids are tissue hormones synthesized from long-chain polyunsaturated fatty acids, mainly arachidonic acid (AA) (Sales *et al*., 2008). Phospholipase A_2 (PLA_2), and to be more precise cytoplasmic phospholipase A_2 ($cPLA_2$), is the first enzyme engaged in synthesizing these compounds, as it specifically releases AA from lipids in the cell membrane, which then enters cyclooxygenase pathways (Fig. 1) (Linkous & Yazlovitskaya; 2010).

The two main COX isoforms are cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Both transform AA into prostaglandin H_2 (PGH_2), which then again transformed by proper synthases, mainly cytosolic prostaglandin E synthase (cPGES), microsomal prostaglandin E synthase-1 (mPGES-1), microsomal prostaglandin E synthase-2 (mPGES-2), prostaglandin I synthase (PGIS), and thromboxane synthase (TxS) into prostaglandins (PGs) and thromboxanes.

The *COX-1* gene is principally constitutive in function and possesses a typical, GC-rich housekeeping promoter. In contrast, the *COX-2* gene resembles an early response gene. It is strongly induced by mitogenic and proinflammatory stimuli, superinduced by inhibitors of protein synthesis, and acutely regulated at both transcriptional and posttranscriptional levels (Lasa *et al*., 2000).

The prostanoids of noteworthy biological significance include: prostaglandin E_2 (PGE_2), prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), prostaglandin D_2 (PGD_2), 15d-PGJ_2, PGI_2, and TxA_2. PGE_2 is an important proinflammatory prostaglandin revealing antiapoptotic properties, which plays essential functions in renal physiology, the physiology of the immune system and is a developmental and growth factor associated with neoplasms (Harris, 2013). While $PGF_{2\alpha}$ is synthesized in the uterine wall and plays a crucial role not only in the physiology of this organ, it is also an autocrine growth factor in connection with endometrial adenocarcinoma (Sales *et al.,* 2008; Woodward *et al.,* 2011). A dehydrated derivative of PGD_2 (15d-PGJ_2) is a principal prostaglandin which inhibits prostanoid synthesis and the intensity of inflammatory reactions (Surh *et al.,* 2011). Other important products of arachidonic acid transformations include TxA_2 and PGI_2, synthesized by COX-1 and COX-2, respectively (Catella-Lawson *et al.,* 1999). Both these prostanoids play important roles in the physiology and pathology of blood vessels (Caughey *et al.,* 2001; Debey *et al.,* 2003; Meyer-Kirchrath *et al.,* 2004). TxA_2 causes the aggregation of blood platelets and the contraction of blood vessels, whereas PGI_2 has opposite properties.

PROSTANOID SYNTHESIS IN THE COURSE OF INFLAMMATORY RESPONSE

Prostanoids play a chief role in inflammatory reactions. The synthesis of these compounds differs depending on the inflammatory reaction phase. During the first hours after the activat on by a the proinflammatory sub-

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Abbreviations: 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; 15d-PGJ_2, 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2; AA, arachidonic acid; AC, adenylate cyclase; AP-1, activator protein 1; CaMK-II, Ca^{2+}/calmodulin-dependent protein kinase II; CBP, CREB-binding protein; COX, cyclooxygenase; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; $cPLA_2$, cytoplasmic phospholipase A_2; CRE, cAMP response element; CREB, cAMP response element-binding protein; CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells; DP, prostaglandin D_2 receptor; EGFR, epidermal growth factor receptor; eNOS, endothelial nitric oxide synthase; EP, prostaglandin E_2 receptor; ERK1/2, extracellular-signal-regulated kinases 1 and 2; FP, prostaglandin $F_{2\alpha}$ receptor; GRK, G protein-coupled receptor kinases; IKK, IκB kinase; IKKβ, IκB kinase subunit β; IP, prostaglandin I_2 receptor; IP_3, inositol trisphosphate; JNK, c-Jun N-terminal kinase; KO, knockout; LPS, lipopolysaccharides; MAPK, mitogen-activated protein kinase; mPGES, microsomal prostaglandin E synthase; MRP4, multidrug resistance-associated protein 4; NF-κB, nuclear factor κB; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; PGIS, prostaglandin I synthase; PGT, prostaglandin transporter; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA, protein kinase A; PKB, protein kinase B; PKC, protein kinase C; PLA_2, phospholipase A_2; PLCβ, phospholipase Cβ; PPARγ, peroxisome proliferator-activated receptor γ; PTEN, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase; ROS, reactive oxygen species; $sPLA_2$, secreted phospholipase A_2; TP, thromboxane A_2 receptor; TPα, thromboxane A_2 receptor α isoform; TPβ, thromboxane A_2 receptor β isoform; TxA_2, thromboxane A_2; TxS, thromboxane synthase.

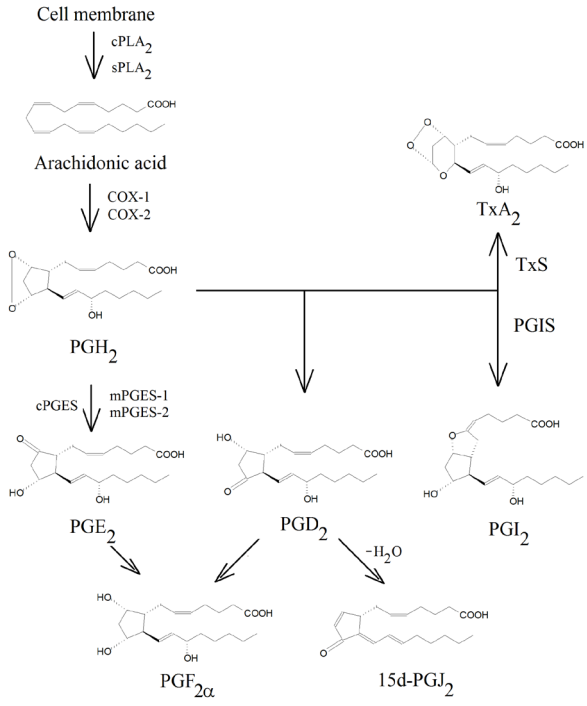

Figure. 1. COX pathways.
Arachidonic acid is released from cell membrane by $cPLA_2$. In can then undergo transformations by cytochrome P450, lipoxygenases or COX. The latter enzymes transform arachidonic acid into PGH_2. The newly formed prostaglandin is transformed into other prostaglandins or TxA_2 by appropriate synthases.

stance COX-2 expression increases and $cPLA_2$ is activated, which leads to increased PGH_2 synthesis (Murakami *et al.,* 1997). However, a simultaneous lack of mPGES-1 expression, transforming PGH_2 into PGE_2, results in a coincident increase of PGD_2 synthesis (Xiao *et al.,* 2012). Nonetheless, the COX-2 expression in this phase does not depend on the autocrine activation by PGE_2 (Murakami *et al.,* 1997).

During the second phase, lasting for 12 to 48 hours after the stimulation, mPGES-1 and $cPLA_2$ expression takes place, which intensifies PGE_2 synthesis (Murakami *et al.,* 1997; Xiao *et al.,* 2012) with an unchanged synthesis of PGD_2 (Xiao *et al.,* 2012). Expression of COX-2 and $cPLA_2$ undergoes autocrine stimulation by PGE_2, but there is no simultaneous influence of this compound on the expression of mPGES-1 (Murakami *et al.,* 1997; Xiao *et al.,* 2012). The addition of inhibitors of COX-2 and/or $cPLA_2$ results in a simultaneously decreased expression of both enzymes (Murakami *et al.,* 1997; Xiao *et al.,* 2012), while adding PGE_2 suppresses the effect of these inhibitors on the COX-2 and $cPLA_2$ expression (Murakami *et al.,* 1997). Besides, in the course of this inflammatory phase, depending on its duration, the expression of COX-2 can be hampered by 15d-PGJ_2 (Inoue *et al.,* 2000).

DYSREGULATION OF THE PROSTANOID SYNTHESIS PATHWAY IN NEOPLASTIC DISEASES

PGE_2 plays an important role in cancer development. It shows antiapoptotic activity and supports angiogenesis, which is why it could be a promising target in an antineoplastic therapy (Greenhough *et al.,* 2009).

The pathways of prostanoid synthesis tend to become dysregulated with the progression of a neoplastic disease (Table 1). First of all, the expression of COX-2 and mPGES-1 is increased and consequently the intensity of PGE_2 production increased (Badawi & Badr, 2003; Nakanishi *et al.,* 2008). Apart from the amplifying inflammatory reactions, the anti-inflammatory mechanisms are dysregulated. Expression of peroxisome proliferator-activated receptor γ (PPARγ), which participates in the inhibition of inflammatory reactions, is decreased due to an increased COX-2 expression (Inoule *et al.,* 2000). Also the synthesis of 15d-PGJ_2 decreases as a result of the rise in mPGES-1 expression (Badawi & Badr, 2003). The expression of mPGES-1 causes an increased PGE_2 synthesis, as mentioned above, at the cost of PGD_2, which leads not only to the deactivation of the function of 15d-PGJ_2, but also supports angiogenesis and the progress of neoplastic diseases (Murata *et al.,* 2011; Davoine *et al.,* 2013).

The changes in the prostanoid synthesis in neoplastic cells occur along with changes in the enzymes degrading those compounds. Neoplastic cells reveal an entire lack or a decreased expression of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a PGE_2 degrading enzyme (Wolf *et al.,* 2006; Jang *et al.,* 2008; Lee *et al.,* 2013). The mechanism underlying the expression disorders of 15-PGDH may partially result from the increased expression of COX-2 (Tong *et al.,* 2006). In colorectal neoplasia a lowered expression of the prostaglandin transporter (PGT) participating in uptaking PGs is often noted, as well as an increased expression of multidrug resistance-associated protein 4 (MRP4) taking part in the secretion of PGs from the cell (Holla *et al.,* 2008). Furthermore, the expression of prostaglandin receptors also increases. An increased expression of prostaglandin E_2 receptor-4 (EP_4) has been observed, among others, on colorectal neoplastic cells (Chell *et al.,* 2006). All these changes result in an increased concentration of PGE_2 in the surroundings of neoplastic cells. This causes an autocrine activation of neoplastic development and the progress of the disease.

INFLAMMATORY REACTION POSITIVE FEEDBACK LOOP INVOLVING PROSTAGLANDIN E_2

COX-2 expression is in a positive feedback loop with its products a PGE_2 and $PGF_{2\alpha}$ (Inoule *et al.,* 2000; Sales *et al.,* 2001; 2008). This process is of considerable significance as far as autocrine support of inflammatory reactions and activation of neoplastic cells' growth (Sales *et al.,* 2001; 2008). The mechanism associated with the way prostaglandins influence COX-2 expression consists in increasing the COX-2 mRNA stability and in activating the *COX-2* gene promoter (Sales *et al.,* 2008). Both these processes depend on the type of cells (Inoule *et al.,* 2000; Sales *et al.,* 2001; 2008).

PGE_2 increases the expression of COX-2 acting through its receptors, prostaglandin E_2 receptor-2 (EP_2) and EP_4, which activate adenylate cyclase (AC), and this increases the concentration of cAMP in the cell (Sakuma *et al.,* 2004). In turn, cAMP increases the stability of COX-2 mRNA and activates *COX-2* promoter by means of protein kinase A (PKA) and cAMP response element-binding protein (CREB) (Inoule *et al.,* 2000; Sales *et al.,* 2001; Fujino *et al.,* 2005; Díaz-Muñoz *et al.,* 2012).

Activated EP_4 also activates phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), which causes a PKA-independent signal transduction to CREB (Fujino *et al.,* 2005).

Table 1. Prostanoid pathway compounds under three conditions.
Comparison of three conditions: normal condition, inflammation caused by a pro-inflammatory factor, and cancer

Trait	Normal condition	Inflammation	Cancer cell
COX-2 protein expression	none	present	present
mPGES-1 protein expression	none	present	present
PGE_2 level	low	high	high
15-PGDH protein expression	high	low	none
PGD_2 level	normal	high	low
15d-PGJ_2 level	normal	high	low

PGE_2 also increases COX-2 expression by activating mitogen-activated protein kinase (MAPK) cascades (Faour *et al.,* 2001; Rösch *et al.,* 2005). EP_4 uses PI3K to activate the extracellular-signal-regulated kinases 1 and 2 (ERK1/2) MAPK cascade, leading to increased COX-2 expression (Fujino *et al.,* 2003; 2005; Mendez & LaPointe, 2005; Rösch *et al.,* 2005; Sales *et al.,* 2008). Protein kinase C (PKC) and Ca^{2+} can also participate in the activity of PGE_2 (Rösch *et al.,* 2005). The additionally activated EP_4 receptor, through a pathway independent of PKA, activates the p38/MAPKAPK-2/hsp 27 cascade which is responsible for increasing the stability of COX-2 mRNA (Lasa *et al.,* 2000; Faour *et al.,* 2001; Rösch *et al.,* 2005). The stability of COX-2 mRNA is enhanced by preventing its degradation from the 3'-untranslated region of mRNA rich in AU nucleotides (Lasa *et al.,* 2000; Faour *et al.,* 2001).

DEGRADATION PATHWAY OF PROSTAGLANDIN E_2

After synthesis PGE_2, is secreted outside the cell by MRP4. During the following phase, it can be uptaken by PGT and degraded in the cytoplasm (Fig. 2) (Vezza *et al.,* 2001). This particular transporter specifically transports not only PGE_2, but also PGD_2 and $PGF_{2\alpha}$ (Vezza *et al.,* 2001). This is followed by the degradation of PGE_2 in the cytoplasm by 15-PGDH into an inactive 15-keto-PGE_2 form (Holla *et al.,* 2008). Products of COX transformations take part in regulating the PGE_2 degradation pathway.

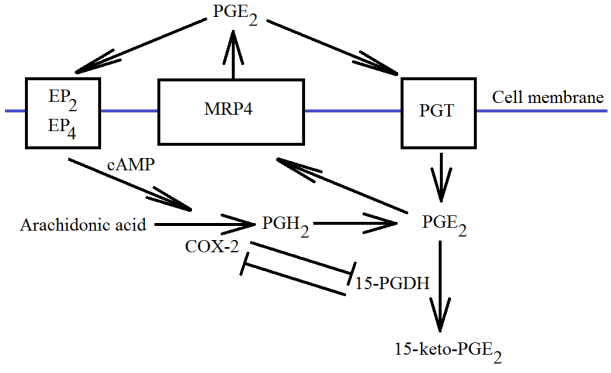

Figure 2. PGE_2 degradation.
PGE_2 is secreted from cells by MRP4. Outside the cells, PGE_2 activates its receptors EP_2 and EP_4, thus increasing COX-2 expression. It may also undergo uptake by means of PGT in the cytoplasm, PGE_2 is degraded by 15-PGDH to 15-keto-PGE_2. COX-2 and 15-PGDH, the key enzymes in the synthesis and degradation of PGE_2, mutually inhibit each other's their expression, an increase in the expression of one enzyme leads to reduced expression of the other.

An activated prostaglandin $F_{2\alpha}$ receptor (FP) reduces the PGT activity, and hence the uptake of prostaglandin through this transporter is reduced (Vezza *et al.,* 2001). This regulation occurs through the G_s protein, but is independent of AC (Vezza *et al.,* 2001). Additionally, the levels of COX-2 and 15-PGDH expressions are directly related to each other. Increased expression of one enzyme inhibits the expression of the other one (Tong *et al.,* 2006; Liu *et al.,* 2008). Nevertheless, the dependence between the expression of both enzymes is independent of their activity. Adding an inhibitor of one enzyme does not affect the expression of the other (Tong *et al.,* 2006). The mechanism interconnecting the levels of COX-2 and 15-PGDH expression remains unclear. Most probably 15-PGDH is capable of binding 3'-untranslated region of mRNA COX-2 and, thereby destabilizing it (Tong *et al.,* 2006). The reciprocal influence of COX-2 on 15-PGDH expression, is even less well understood and is still being that examined in order to understand the regulation of expression of these enzymes in neoplastic cells, where COX-2 overexpression and reduced 15-PGDH expression is observed.

MECHANISMS OF PROSTAGLANDIN $F_{2\alpha}$-INDUCED CYCLOOXYGENASE-2 EXPRESSION

$PGF_{2\alpha}$ is yet another prostanoid with a crucial role in the regulation of the synthesis of the prostanoids discussed in this review. It increases the expression of COX-2 through its receptor (FP) and hence increases its own synthesis (Sales *et al.,* 2008). The autocrine activation of this enzyme's expression by $PGF_{2\alpha}$ is of considerable importance for the growth and development of endometrial adenocarcinoma. When present in concentrations reaching 100 nM $PGF_{2\alpha}$ may even activate EP_2 (Fig. 3), leading to the same signal transduction as that caused by PGE_2 (Sales *et al.,* 2008). FP activates phospholipase Cβ (PLCβ) which releases inositol trisphosphate (IP_3) and diacylglycerol (Sales *et al.,* 2008; Woodward *et al.,* 2011) which activate PKC, however, this pathway will not induce the expression of COX-2 protein (Sales *et al.,* 2008). $PGF_{2\alpha}$ binds to FP, that caused signal transduction, which activates ERK1/2 MAPK and hence results in COX-2 expression (Jabbour *et al.,* 2005; Sales *et al.,* 2008).

Whilst PLCβ activates ERK1/2 MAPK by means of epidermal growth factor receptor (EGFR), which leads to expression of COX-2 (Sales *et al.,* 2004; 2008), it seems that also PKA also participates in transducing signals from FP to ERK1/2 MAPK (Sales *et al.,* 2008). As for EGFR activation, c-Src and metalloproteinases may also participate in this process (Sales *et al.,* 2005). It has also been shown that the upregulation of COX-2 expression results from activating CREB and ac-

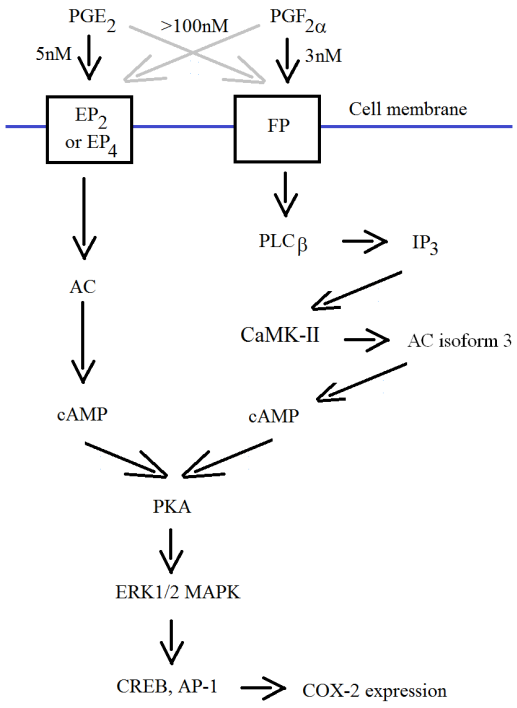

Figure 3. Mechanism of COX-2 expression stimulation by PGE_2 and $PGF_{2\alpha}$.
Both prostaglandins activate their respective receptors: EP_2, EP_4 and FP. At larger levels of the order of 100 nM, PGE_2 is also capable of activating the FP receptor. EP_2 and EP_4 cause activation of AC and transduction of the signal to PKA. At the same time, FP activates PLCβ, products of which are involved in activation of PKC causing influx of calcium ions. This may have a synergistic effect in the EP_2 and EP_4-mediated activation of AC. Eventually, the signal is transducted to ERK1/2 MAPK, leading to activation of *COX-2* promoter by CREB and AP-1.

tivator protein 1 (AP-1) by means of ERK1/2 MAPK (Sales *et al.,* 2008).

The affinity of PGE_2 for FP is lower (119 nM) than its affinity for EP_2 (4.9 nM) or EP_4 (0.79 nM) (Abramovitz *et al.,* 2000). In concentrations reaching 100nM, PGE_2 increases the expression of COX-2 not only by its EP_2 and EP_4 receptors but also through FP (Sales *et al.,* 2008). When increasing the expression of COX-2, activated EP and FP receptors act synergistically, as they activate ERK1/2 MAPK through PKA (Sales *et al.,* 2008). The calcium influx, dependent on IP_3, activates Ca^{2+}/calmodulin-dependent protein kinase II (CaMK-II) and ultimately the transmission of signal to Ca^{2+} dependent AC isoform 3 (Abera *et al.,* 2010). The cross-activation of EP and FP receptor by PGE_2 and $PGF_{2\alpha}$ is crucial in neoplastic cells expressing FP as in endometrial adenocarcinoma (Sales *et al.,* 2008; Woodward *et al.,* 2011). The both prostaglandins increase COX-2 expression, which results in an autocrine upregulation of their level. This, again, leads to the development and growth of the neoplasm (Sales *et al.*, 2005; 2008).

15-DEOXY-$\Delta^{12,14}$-PROSTAGLANDIN J_2 AS AN ANTI-INFLAMMATORY REGULATOR OF PROSTANOID SYNTHESIS

Apart from the above-mentioned PGE_2 and $PGF_{2\alpha}$, other prostaglandins also exert an autocrine influence on prostanoid synthesis. 15d-PGJ_2 is a prostanoid regulating the intensity of inflammatory reactions and reducing the pace of neoplastic growth and development (Surh *et al.*, 2011). It is formed by non-enzymatic dehydration of PGD_2 (Surh *et al.*, 2011).

By means of their receptors, respectively EP_2 and EP_4, as well as the prostaglandin D_2 receptor (DP), PGE2 and PGD_2 increase the cAMP concentration and thereby enhance the expression of COX-2 protein (Sakuma *et al.,* 2003). After a certain period of time, however free PGD_2 becomes dehydrated to 15d-PGJ_2, which in low concentrations reduces the expression of COX-2 protein (Surh *et al.,* 2011) through a pathway that can be dependent or independent on the PPARγ receptor (Fig. 4) (Inoule *et al.,* 2000; Sawano *et al.,* 2002). In cells treated with a proinflammatory factor, the activated PPARγ receptor disturbs the induction of COX-2 protein expression along various routes. In particular, it disturbs the activation of nuclear factor κB (NF-κB) (Inoule *et al.,* 2000). Additionally, PPARγ disrupts the activation of the AP-1 transcription factor by means of c-Jun N-terminal kinase (JNK) MAPK and binds, and thereby inactivates, CREB-binding protein (CBP)/p300 (Subbaramaiah *et al.,* 2001). It has also been shown that 15d-PGJ_2 inhibits signal transduction through ERK1/2 and JNK MAPK into AP-1, along a pathway independent of PPARγ receptor (Sawano *et al.,* 2002). Additionally, 15d-PGJ_2 inhibits the activation of NF-κB by restraining the activity of IκB kinase subunit β (IKKβ) by modifying its cysteine residues (Boyault *et al.,* 2004). The disrupted phosphorylation precludes the degradation of the NF-κB inhibitor: IκBα (Boyault *et al.,* 2004). Apart from that, 15d-PGJ_2 modifies cysteine residues in the DNA binding domain on p65 NF-κB, which leads to its inactivation (Straus *et al.,* 2000; Boyault *et al.,* 2004).

The molecular mechanism of the modification of cysteine residues by 15d-PGJ_2 is well known. The arrangement of atoms in the 15d-PGJ_2 ring creates an

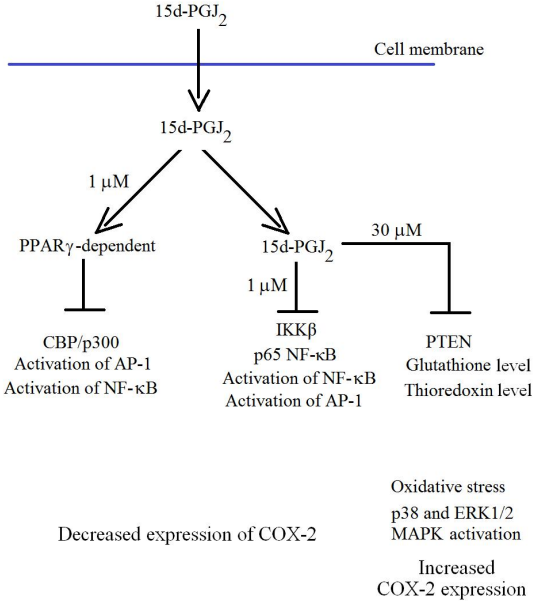

Figure 4. Effects of 15d-PGJ_2 on COX-2 expression.
15d-PGJ_2 undergoes cytoplasmic uptake and activates its receptor PPARγ. This leads to inhibition of the activity of NF-κB, JNK MAPK and CBP/p300. Another pathway of 15d-PGJ_2 activity is direct inhibition of p65 NF-κB and IKKβ. Both pathways decrease COX-2 protein expression. At very large levels, 15d-PGJ_2 deactivates antioxidants containing free –SH groups. By this mechanism, it sensitizes the cells to the effects of ROS, which may lead to an increase in COX-2 protein expression.

Table 2. Properties of the prostanoids receptors.
The receptors are categorized by their ligands and activated pathways. The main activated enzymes are AC or PLC. Receptors are desensitized or internalized following phosphorylation by PKC, PKA and GRK.

Receptor	Ligand	Main activation effect	PKA activation	PKC activation	Receptor desensitization/internalization pathway
EP_1	PGE_2	PLC, ↑Ca^{2+}, no IP_3	–	+	PKC
EP_2	PGE_2	AC, ↑cAMP	+	–	Not affected
EP_3	PGE_2	AC, ↓cAMP	–	–	GRK($EP_{3\alpha}$)
EP_4	PGE_2	AC, ↑cAMP, PI3K	+	–	GRK, PKC*
DP	PGD_2	AC, ↑cAMP, ↑Ca^{2+}	+	–	PKC*, GRK
CRTH2	PGD_2	AC, ↓cAMP, ↑Ca^{2+}	–	+	PKC, PKA*, GRK
IP	PGI_2	AC, ↑cAMP, PLC	+	+	PKC, PKA(AC isoform 5 and 6)
FP	$PGF_{2\alpha}$	PLC, ↑Ca^{2+}	–	+	PKC(FP_A), constitutive FP_B,
TP	TxA_2	PLC, ↑Ca^{2+}	–	+	GRK, PKA(TPα)*, PKC

*cross-desensitization/internalization pathway triggered by an other type of receptor

electrophilic carbon (Straus *et al.,* 2000) which undergoes Michael addition with cysteine residues (R-SH) (Straus *et al.,* 2000). The reaction with cysteines in the catalytic centre, can lead to the inactivation of an enzyme, such as IKKβ. As a consequence, this evokes the reduction of COX-2 protein expression.

Moreover, 15d-PGJ_2 affects the expression of COX-2 through mechanisms related to the synthesis of reactive oxygen species (ROS), since at low concentrations 15d-PGJ_2 activates cellular defense mechanisms against ROS and at the same time increases the concentration of antioxidants, e. g., glutathione (Koppal *et al.,* 2000). It also increases the level of heme oxygenase 1 expression (Koppal *et al.,* 2000). An increased level of antioxidants in the cell disrupts signal transduction along pathways where ROS function as second messengers. This disturbes transduction of NF-κB activation signals and activation of MAPK kinase cascades responsible for COX-2 expression (Koppal *et al.,* 2000).

Paradoxically, at high concentrations 15d-PGJ_2 may actually increase the expression of COX-2. In breast cancer cells, 30 μM 15d-PGJ_2, increases the expression of COX-2 by inhibiting the activity of phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase (PTEN) (Kim *et al.,* 2008). This causes the activation of protein kinase B (PKB) and, signal transduction upregulating COX-2 expression (Kim *et al.,* 2008). 15d-PGJ_2 can also activate p38 MAPK and, by means of EGFR, also of the ERK1/2 MAPK cascade, which leads to the induction of mRNA *COX-2* synthesis and also increases its stability (Kitz *et al.,* 2011). This mechanism resembles the route by which COX-2 expression is induced by ROS.

15d-PGJ_2 and ROS reveal a similar activity in relation to enzymes, by modifying cysteine residues in their catalytic centres. ROS create disulphide bonds or sulfenic acid (Cys-SOH), which often inhibits the activity of enzymes with a cysteine in their catalytic centre (Meng & Zhang, 2013). When 15d-PGJ_2 reacts with a cysteine residue, it also inhibits the activity of enzymes (Straus *et al.,* 2000; Boyault *et al.,* 2004). This is why the both compounds can have similar effects when present at high concentrations. Additionally, 15d-PGJ_2 inactivates glutathione and thioredoxin, sensitizing the cell to oxidative stress and second messengers, such as ROS (Shibata *et al.,* 2003; Kim *et al.,* 2008). This effect may be relieved by increasing the concentration of antioxidants with free R-SH groups which react directly with 15d-PGJ_2 (Kim *et al.,* 2008).

The regulation of COX-2 expression is a dynamic process. On one hand it is inhibited by the PGD_2 metabolite 15d-PGJ_2, while on the other it is activated by PGE_2. The two prostanoids, 15d-PGJ_2 and PGE_2, form a more complex system of interdependencies. Following the treatment of cells with an inflammatory factor, such as lipopolysaccharides (LPS), the level of PPARγ is reduced, which leads to partial deactivation of 15d-PGJ_2 and simultaneously to increased expression of COX-2 (Inoule *et al.,* 2000). Conversely, blocking the activity of mPGES-1, an enzyme collaborating with COX-2 in the reduction of PGE_2, increases expression of PPARγ (Kapoor *et al.,* 2007). This effect is caused by signal transduction from the PGE_2 receptor to PI3K and PKB, which in turn inhibit the expression of PPARγ (Kapoor *et al.,* 2007).

LIGAND-MEDIATED DESENSITIZATION AND INTERNALIZATION OF RECEPTORS

Desensitization means reducing the sensitivity of a receptor in response to a prolonged exposure to a given ligand. This process plays an important role in the physiology of receptors, especially when reducing the cellular response to a particular factor, which may become too intense.

Exposure to PGE_2 results in internalization and desensitization of EP_4 receptor, whilst EP_2 maintains its sensitivity towards PGE_2 (Table 2) (Desai *et al.,* 2000). The C-tail plays a key role in desensitization of EP_4, as it is phosphorylated by G protein-coupled receptor kinases (GRK) (Desai *et al.,* 2000; Slipetz *et al.,* 2001). Throughout this process, PKA does not exert any influence on the EP_4 (Neuschäfer-Rube *et al.,* 1999; Slipetz *et al.,* 2001). PKC is able to influence EP_4, but this kinase is not activated by EP_4 receptor (Neuschäfer-Rube *et al.,* 1999; Slipetz *et al.,* 2001). As far as the rat prostaglandin E_2 receptor-3 (EP_3) is concerned, $EP_{3\alpha}$ undergoes desensitization by phosphorylation dependent on GRK,

whereas $EP_{3\beta}$ does not (Neuschäfer-Rube *et al.,* 2005). Prostaglandin E_2 receptor-1 (EP_1) undergoes desensitization and internalization following of phosphorylation by PKC (Katoh *et al.,* 1995).

Aside from EP, other receptors also undergo desensitization and internalization. Receptors for $PGF_{2\alpha}$ are present in two isoforms: FP_A and FP_B. $PGF_{2\alpha}$ causes internalization of FP_A dependent on PKC, while FP_B undergoes partial, constitutive internalization independent of the ligand, since there are no phosphorylation sites for PKC in its C-tail (Srinivasan *et al.,* 2002).

PGD_2 has two receptors: DP and chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). Both these receptors have a C-tail susceptible to phosphorylation, which is essential for their internalization (Gallant *et al.,* 2007; Schröder *et al.,* 2009; Roy *et al.,* 2010). CRTH2 undergoes the internalization through phosphorylation with PKC and a GRK: GRK2, GRK5 and/or GRK6 (Roy *et al.,* 2010). DP internalization depends on PKC, but this kinase is not activated by DP (Gallant *et al.,* 2007). What is more, DP internalization depends only on GRK2 and not depend on GRK5 or GRK6 (Gallant *et al.,* 2007). Another difference between these two receptors lies in the fact that the internalization of CRTH2 depends on the activation of PKA (Gallant *et al.,* 2007). However, when this kinase is activated but CRTH2 is not, it does not result in the internalization of the receptor (Gallant *et al.,* 2007). The internalization of the receptors for PGD_2 also depends on arrestins: that of DP on arrestin-2 and -3, and of CRTH2 on arrestin-3 only (Gallant *et al.,* 2007; Schröder *et al.,* 2009; Roy *et al.,* 2010).

PROSTAGLANDIN SYNTHESIS COMPENSATION IN CELLS WITH DISTURBED OF CYCLOOXYGENASE PATHWAYS

Gene knockout (KO) can serve as a model for the chronic use of COX inhibitors. Dysruption of either *COX* gene, *COX-1* or *COX-2*, upregulates PGE_2 synthesis in cultured cells (Table 3) (Kirtikara *et al.,* 1998; Kanekura *et al.,* 2002). Cells with *COX-1* or *COX-2* defects show an increased expression of $cPLA_2$, secreted phospholipase A_2 ($sPLA_2$), mPGES-1, as well as the second, functional *COX* isoform, but they also exibit by a decreased expression of mPGES-2 (Kirtikara *et al.,* 1998; Zhang *et al.,* 2002; Bosetti *et al.,* 2004; Choi *et al.,* 2006; Sandee *et al.,* 2009). *COX-2* KO cells do not respon to proinflammatory factors (Kirtikara *et al.,* 1998). In the mouse brain with a *COX-2* knockout it a decreased concentration of PGE_2 is observed due to a non fully compensating increased COX-1 protein expression (Bosetti *et al.,* 2004). In macrophages, the COX-2 defect causes an increase in the expression of 5-lipoxygenase (Zhang *et al.,* 2002; Bosetti *et al.,* 2004).

Table 3. Prostanoid synthesis in *COX* KO cells.
COX KO cells are characterized by increased production of PGE_2, expression of phospholipase A_2 and of the other COX isoform.

Trait	*COX-1* KO	*COX-2* KO
PGE_2 production	↑	↑
$cPLA_2$ expression	↑	↑
$sPLA_2$ expression	↑	↑
COX-1 expression		↑
COX-2 expression	↑	
In brain		
PGE_2 concentration	↑	↓
mPGES-2 expression	↓	↓
NF-κB activation	↑	↓

Due to the production of TxA_2 by COX-1, the lack of this enzyme decreases the level of this eicosanoid as well as the level of TxS expression (Choi *et al.,* 2006). On the other hand, expression of COX-2 and synthesis of PGE_2 occurring under the influence of a proinflammatory factor in *COX-1* KO mice was higher when compared with wild-type cells (Kirtikara *et al.,* 1998).

In brains of *COX-1* KO mice the PGE_2 synthesis increases, as does COX-2 expression, which is caused by the activation of NF-κB (Kanekura *et al.,* 2002; Choi *et al.,* 2006). This activation is due to an increased expression of NF-κB (subunits p50 and p65) and next to constant activation of IκB kinase (IKK) (Choi *et al.,* 2006). In contrast in *COX2*-KO animals, the basal level of NF-κB activaty is decreased (Rao *et al.,* 2005). In brain cells with *COX2* KO the PGE_2 concentration is decreased, which may lead to reduced activation of NF-κB (Poligone & Baldwin, 2001; Rao *et al.,* 2005; Choi *et al.,* 2006). Nevertheless, the exact mechanisms underlying the interdependence of COX-1 and COX-2 expressions require a more thorough research. It seems that the both enzymes inhibit their own expressions, and the lack of one causes a compensating increase in the expression of the second. Probably the expression of one COX isoform depends on the presence of mRNA or the protein of the other isoform. Another possibility is that products of COX pathways affect the expression of the other COX isoform.

Due to the pro-neoplastic character of the products of AA transformations by COXs and lipoxygenases, recent studies focus on the mechanisms of the inhibition of expression and activity of $cPLA_2\alpha$. In the course of inflammatory reactions, this enzyme releases AA from cell membranes lipids. Inhibiting the $cPLA_2\alpha$ activity simultaneously inhibits the activity of COX and lipoxygenases. In mouse brain, *cPLA2a* KO leads to a reduction in COX-2 expression, which then effects in lower PGE_2 synthesis, while the expression of COX-1 and 5-lipoxygenase is unaffected (Bosetti & Weerasinghe, 2003; Sapirstein *et al.,* 2005). A decreased COX-2 expression may result from the inhibition of platelet-activating factor (PAF) synthesis (Serou *et al.,* 1999; Bosetti & Weerasinghe, 2003). PAF activates p38 and ERK1/2 MAPK, which increase the expression of COX-2 (Serou *et al.,* 1999). The expression of COX-2 is induced throught the proinflammatory factor. In mice with *$cPLA_2a$* defect, the expression of COX-1 decreases after proinflammantory factor treatment, while the induction of COX-2 expression and production of PGE_2 are disturbed (Sapirstein *et al.,* 2005). In contrast in prostate cancer models blocking the $cPLA_2\alpha$ activity leads to increased expression of COX-1 and PGE_2 production, with no changes in COX-2 expression. Additionally, the secretion of lipoxygenase transformation products is reduced. Adding 5- and/or 12-hydroxyeicosatetraenoic acid, products of lipoxygenases transformations, reduced the level of COX-1 expression and PGE_2 production (Niknami *et al.,* 2010).

Inhibiting the activity of mPGES-1, an enzyme engaged in the production of PGE_2 dependent on COX-

2, could be used as a therapeutic strategy in neoplasms. *mPGES-1* KO disturbes the synthesis of PGE_2 and other products of COXs pathways. Enzymatic defects in mPGES-1, reducing in the production of PGE_2 may be organ specific, e.g.,. they may concern solely the brain or the stomach. Simultaneosly the production of PGI_2, TxA_2 and PGD_2 in the digestive system is increased (Boulet *et al.,* 2004; Elander *et al.,* 2008).

During the stimulation of the inflammatory reaction in *mPGES-1*-KO mice the synthesis of TxA_2, PGI_2, $PGF_{2\alpha}$ and PGD_2 is increased, as is the expression of COX-2, when compared to cells with functional mPGES-1 (Boulet *et al.,* 2004; Trebino *et al.,* 2005; Brenneis *et al.,* 2008; Elander *et al.,* 2008), most likely to compensate for the diminished level of PGE_2. The compensatory mechanisms is probably not connected with changes in the expression of particular synthases, but rather with the availability of PGH_2 (Boulet *et al.,* 2004). Since there is no mPGES-1 expression, PGH_2 is available for transformation to proper prostanoids by other synthases. Application of mPGES-1 inhibitors in neoplastic therapy in order to limit the synthesis of PGE_2 can thus cause an increased synthesis of other proneoplastic prostanoids, and as a consequence lead to effects contrary to those intended (Elander *et al.,* 2008).

THE IMPACT OF THROMBOXANE A_2 AND PROSTAGLANDIN I_2 ON PROSTANOID SYNTHESIS PATHWAY

TxA_2 and PGI_2 increase COX-2 expression, which leads to increased PGI_2 synthesis in blood vessels. Upon PGI_2 binding, prostaglandin I_2 receptor (IP) upregulates cAMP synthesis, which induces COX-2 expression in the smooth muscles of blood vessels (Debey *et al.,* 2003; Sakuma *et al.,* 2003; Meyer-Kirchrath *et al.,* 2004). Increased expression of cAMP inducible early repressor occurs along with the increased COX-2 expression (Debey *et al.,* 2003). This transcriptional repressor binds cAMP response element-binding protein (CREB), and decreases the expression of genes including *COX-2* (Debey *et al.,* 2003).

TxA_2 affects the expression of COX-2 by a different mechanism. Due to its instability, TxA_2 functions only locally (Miyosawa et al., 2006). TxA_2 binding to thromboxane A_2 receptor (TP) activates PLCβ without affrcting cAMP concentration. (Sakuma *et al.,* 2003; Woodward *et al.,* 2011). PLCβ causes the induction of COX-2 expression through ERK1/2 MAPK and thus increases the synthesis of PGE_2 and PGI_2 in blood vessel cells (Caughey *et al.,* 2001; Chu *et al.*, 2003). The activation of ERK1/2 MAPK through ligand-activated TP is complex process involving PKC, PKA and PI3K (Miggin & Kinsella, 2002b).

Expression of COX-2 and synthesis of PGI_2 can suppress the activity of TxA_2 in prolonged exposure to this thromboxane. The detailed mechanism associated with activating the expression of COX-2 is very well known. One can distinguish two isoforms of receptors for TxA_2: thromboxane A_2 receptor isoform α (TPα) and β (TPβ). The difference between these two receptors is associated with their C-tail located at the cytoplasmic side of the cell membrane (Miyosawa *et al.,* 2006). The two isoforms of TP can be associated with diferent G proteins and can therefore activate the MAPK cascade in different manners. Among others, PKA participates in the activation of ERK1/2 MAPK by TPα, but not by TPβ (Miyosawa *et al.,* 2006). The signal transduction pathways depend on the type cell as well as the domination of the described isoforms of the receptor (Miyosawa *et al.,* 2006). Most probably the activation of TPα leads to a minimally increased cAMP concentration to the activation of PKA, whereas the second isoform TPβ has an entirely opposite influence on AC (Hirata *et al.,* 1996). TPα activates ERK1/2 MAPK within several minutes after TxA_2 binding, which is then followed by the deactivation of this cascade of kinases (Miggin & Kinsella, 2002b; Miyosawa *et al.,* 2006). While the other isoform, TPβ, activates ERK1/2 MAPK after a similar period of time, this is a long-lasting process, since an hour later the phosphorylation of ERK1/2 MAPK is still present (Miggin & Kinsella, 2002b; Miyosawa *et al.,* 2006).

INTERACTIONS BETWEEN THROMBOXANE A_2 AND PROSTAGLANDIN I_2 RECEPTORS

The dimerization or oligomerization of receptors plays an important role in transmitting signals from TP or IP. It does not result in proper signal transduction, but can modulate the properties not only of the receptors, but also of the signals they transmit (Wilson *et al.,* 2004).

Expression of both TP isoforms can lead to the formation of their heterodimer. It probably takes place immediately after the receptors are synthesized and can later cause a reduction of TPα expression (Sasaki *et al.,* 2006). The TP heterodimer differs from the homodimers, because it produces a stronger signal in response to certain agonists (Wilson *et al.,* 2007b). Nevertheless, it is a simplified model, since it seems that TP receptors form both hetero- and homodimers, their oligomerization does not depend on the presence of a ligand (Laroche *et al.,* 2005). Individual receptors in an oligomer are connected with each other by disulphide bonds, which can be split only by reducting factors (Laroche *et al.,* 2005).

Apart from the fact that these two TP isoforms interact with and affect each other, they can also interact with IP. The receptors dimerization (TP and IP) and signal transduction takes place after the activation of these receptors. An activated TPα can dimerize with a nonin-

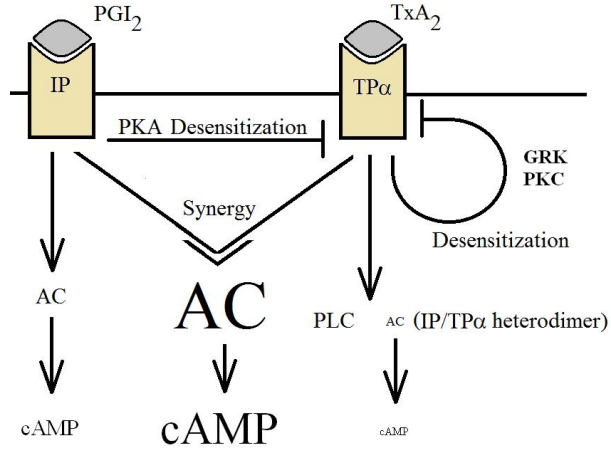

Figure 5. Dependence between IP and TPα.
The two receptors activate different signalling pathways. IP increases cytoplasmic cAMP level by activating AC while TPα activates PLC and AC in IP/TPα heterodimer. Both receptors act synergistically upon AC activation. This is probably due to heterodimerization which alters the signalling pathway activated by TPα. TPα is desensitized by GRK. In addition, ligand-activated IP triggers the same process in TPα by means of PKA.

activated IP and hence transmit a signal similar to that of an activated IP receptor, which means that it causes an increased cAMP concentration (Fig. 5) (Wilson *et al.,* 2004). Yet this process is much more intensified than the sole activity of TPα (Hirata *et al.,* 1996; Wilson *et al.,* 2004). What is more, the activation of both receptors in the IP with TPα-dimer causes a synergistic activation of AC, producing a considerably higher cAMP concentration than IP ialone (Wilson *et al.,* 2004). The cooperation between the two receptors could be of significance as far as the activity of PGI_2 is concerned, as it will suppress the influence exerted by TxA_2 when both these prostanoids are simultaneously present a in blood vessel (Wilson *et al.,* 2004).

Apart from the influence exerted by IP on TP, EP_3 can also increase the intensity of signal transduction from TP. This effect most probably depends on the formation of TP oligomers with EP_3 (Reid & Kinsella, 2009).

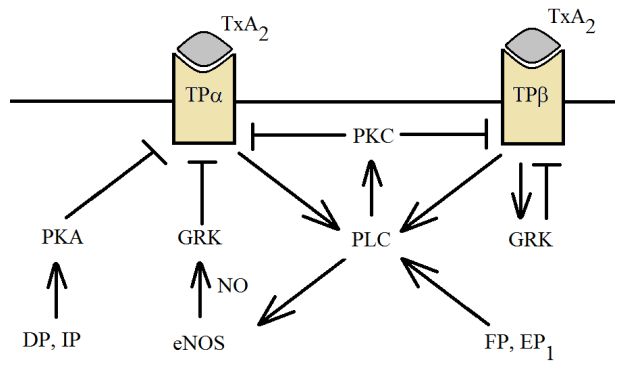

Figure 6. TP desensitization mechanism.
TPα is desensitized by PKC and/or GRK. The activity of GRK towards TPα depends on receptor activation of eNOS. The activity of TPα may also be affected by activation of other prostaglandin receptors that exert their action on TPα *via* PKC or PKA. PKA has no effect on the ligand sensitivity of TPβ. PKC and GRK are involved only in this process. However, GRK-mediated phoshorylation of TPβ is independent of eNOS.

DESENSITIZATION OF RECEPTORS FOR THROMBOXANE A_2 AND PROSTAGLANDIN I_2

The desensitization of receptors for TxA_2 and PGI_2 is of considerable importance in chronic exposure of cells to a large concentration of a certain prostanoid. Iloprost, a PGI_2 homologue, is capable of desensitizing the IP receptor, leading to its internalization (Nilius *et al.,* 2000). In addition to activating AC, IP also activates PLC, which again leads to transduction of signals to PKC (Kam *et al.,* 2001). This could be due to the fact that iloprost acts not only on IP itself, but also has a similar affinity towards EP_1 (Abramovitz *et al.,* 2000; Schermuly *et al.,* 2007). Another possibility is that PLC is activated by IP. Upon phosphorylation of murine IP by PKA, the receptor becomes coupled to G_q and G_i (Lawler *et al.,* 2001; Miggin & Kinsella, 2002a). In contrast, human IP is not coupled to G_i and it activates PLC independently of PKA action (Miggin & Kinsella, 2002a; Chow *et al.,* 2003). Through G_q and G_i, the murine IP receptor activates PLC and inhibits the activity of AC, respectively, which has been confirmed in studies using cicaprost (Lawler *et al.,* 2001). PLC, by means of its product diacylglycerol, then activates PKC. Nonetheless, it seems that the mechanism underlying the activation of PKC depends on the type of cell (Chow *et al.,* 2003). Due to these mechanisms, the ligand is capable of desensitizating IP via PKC which phosphorylates the C-tail of the receptor (Schermuly *et al.,* 2007). As a result IP loses the ability to activate AC. The intensity of the signal transduction from the receptor can also be reduced in another manner. Inhibition of AC isoforms 5 and 6 activity and their expression, which depends on PKA (Sobolewski *et al.,* 2004). This reduces capacity to increase the concentration of cAMP in response to activation occurring through receptors associated with AC. Still, this process is transient and takes place after several hours of exposure to a ligand. After one day of exposure, the initial level and activity of AC isoforms 5 and 6 is restored (Sobolewski *et al.,* 2004).

Activited receptors e.g., IP are once again resensitised to the ligand through endocytosis and recirculation. The described process is important in short-term regulation of receptors activity (Nilius *et al.,* 2000). During long-term exposure to a ligand, internalization and degradation of IP occurs, which does not depend on ist phosphorylation by PKC (Nilius *et al.,* 2000; Smyth *et al.,* 2000). These processes are more intense than *de novo* synthesis and the recirculation of old receptors, leading to a net diminution of IP level (Nilius *et al.,* 2000).

The receptor for TxA_2 undergoes desensitization following phosphorylation by GRK and partially by PKC (Fig. 6) (Flannery & Spurney, 2002). It is a complex process. TPα undergoes phosphorylation by PKC and GRK, and in turn the activity of GRK depends on the activation of endothelial nitric oxide synthase (eNOS) by this receptor and on the transmission of signals to guanylate cyclase (Kelley-Hickie *et al.,* 2007). Activated TPβ undergoes desensitization as well, but here mainly GRK2 and GRK3 carry outwith little involment of the phosphorylation with PKC (Kelley-Hickie & Kinsella, 2006). After the phosphorylation, TPβ undergoes internalization, unlike TPα (Walsh *et al.,* 2000). The internalization of TPβ is a dynamin and arrestin-dependent process (Walsh *et al.,* 2000). Also palmitoylation of the C-tail of the receptor is important, as it provides a proper spatial structure (Reid & Kinsella, 2007).

The cross-desensitization of the TP receptor by PGI_2 is another important process taking place when both TxA_2 and PGI_2. In blood platelets TPα is the main isoform of TP (Habib *et al.*, 1999). It is susceptible to desensitization by PGI_2, which results in suppression of the activity of TxA_2 and makes blood platelets responsive only to PGI_2. PGI_2 and also PGD_2 cause desensitization of TPα through its phosphorylation by PKA (Walsh *et al.,* 2000; Walsh & Kinsella, 2000; Foley *et al.,* 2001; Wikström *et al.,* 2008). EP_1 is yet another receptor with an influence on TP. EP_1 activation causes the desensitization of TPα, and — to a lesser extent — also of TPβ, by PKC (Walsh & Kinsella, 2000). The same process, occurring along the same route, is observed after FP activation (Kelley-Hickie & Kinsella, 2004).

Transmission of the PGI_2 signal can be reduced as a result of internalization of its the receptor IP under the influence of TP activation (Wilson *et al.,* 2007a). Reciprocally, activated IP reduces the amount of TPα in the cell membrane. This process is independent of PKA and most probably involves heterodimerization of IP with TPα and subsequent endocytosis of the dimer (Wilson *et al.,* 2007a).

AUTOREGULATION OF CYCLOOXYGENASE PATHWAYS AND THE FUTURE OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

PGE_2 plays a crucial role in neoplastic processes (Greenhough *et al.,* 2009), therefore a preventive administration of non-steroidal anti-inflammatory drugs (NSAID) reduces the risk of multiple types of neoplasms (Ashok *et al.,* 2011; Johannesdottir *et al.,* 2012). NSAIDs also seem promising anti-neoplastic drugs (Setia *et al.*, 2012). However, inhibiting the activity of COX-2 disturbs the synthesis of PGI_2, therefore new therapeutic solutions are called for (Catella-Lawson *et al.,* 1999; Krotz *et al.,* 2005). Apart from that, inhibiting the activity of COX-2 can cause unexpected results, since the expression of this enzyme is in a negative feedback loop with 15d-PGJ_2 (Inoue *et al.,* 2000). This can lead to prolonged inflammation. Yet another problem is the fact that standard NSAIDs inhibit the activity of COX-2 without any influence on 15-PGDH. Therefore, modern pharmacology faces a challenge of elaboration of new NSAIDs, affecting also the expression of 15-PGDH (Tong *et al.,* 2006; Wakimoto *et al.,* 2008; Tai *et al.,* 2011). In order to accomplish this task, it is essential to fully unrevel the mechanisms of mutual the dependence of COX-2 and 15-PGDH by detailed studies of the autoregulation of cyclooxygenase pathways.

Apart from inhibiting the activity of COX-2, it is also possible to inhibit the activity of mPGES-1, thereby inhibiting PGE_2 synthesis. In colorectal cancer such an approach decreases mass and a reduces the number of polyps formed (Nakanishi *et al.,* 2008). Nonetheless, inhibiting the expression and activity of mPGES-1 may lead to a more intense transformation of PGH_2 into TxA_2, PGI_2, and $PGF_{2\alpha}$ (Trebino *et al.,* 2005; Brenneis *et al.,* 2008; Elander *et al.,* 2008), which stimulate neoplastic cells. That is why, instead of having an anti-neoplastic effect, mPGES-1 inhibitors can actually increased the volume and number of neoplasmatic lesions due to an enhanced production of other eicosanoids (Elander *et al.,* 2008).

Another therapeutic approach consists in using antagonists of EP_2 and EP_4 receptors (Kitamura *et al.,* 2003), due to which a neoplastic cell will produce and secrete large amounts of PGE_2, but the autocrine response to this prostanoid will be disrupted, and this will in turn lead to increased apoptosis and inhibition of cellular divisions.

A chronic administration of specific COX-1 or COX-2 inhibitors or a decreased expression of these enzymes can produce unexpected results. It may increase the level of PGE_2, which is illustrated perfectly by the example of mice with KO of a selected *COX* gene (Bosetti *et al.,* 2004; Choi *et al.,* 2006; Sandee *et al.,* 2009). Inhibiting the expression of COX-2 leads to a compensating increase in the expression of COX-1, which again results in an increased production of PGE_2 (Sandee *et al.*, 2009). Further studies should provide thorough knowledge of the dependence underlying the expression of both isoforms of COX, in order to understand the action and to develop medication capable of influencing the expression of these enzymes.

It has been demonstrated that non-specific inhibitors of COXs in moderate doses can decrease production of TxA_2 by blood platelets, in addition to a having therapeutic effect in the thrombosis (Caughey *et al.,* 2001; Krotz *et al.,* 2005). COX-1 is the main isoform of COX in blood vessels and this particular enzyme is the one that undergoes inhibition, while specific inhibitors of COX-2 result in a decreased production of PGI_2 and hence increase the aggregation of blood platelets (Catella-Lawson *et al.,* 1999; Krotz *et al.,* 2005).

Instead of inhibiting the synthesis of a single prostanoid, it is possible to use another eicosanoid which has an opposite effect. The use of PGI_2 analogues has shown therapeutic effects in patients suffering from thrombosis. In this such an approach balances the effect of TxA_2 without causing the negative consequences connected with its absence (Wilson *et al.,* 2004).

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