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Resolution of Colitis-Associated Inflammation

Hennebert Olivier, Pelissier Marie-Agnès and Morfin Robert
Biotechnologie, CNAM, Paris,
France

1. Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease related to chronic relapsing inflammation of the intestinal tract of unknown aetiology (Podolsky, 2003). Maintenance of colonic inflammation involves a network of inflammatory mediators resulting in a dramatic increase in the production of reactive oxygen species that contribute to the functional change characteristic of UC (Pavlick et al, 2002). Animal models provide evidence that altered cytokine (IL-1β) and eicosanoid secretion patterns may play a role in UC (Blumberg et al, 1999; Stenson, 2007). Eicosanoids, including leukotrienes generated by the 5-lipoxygenase pathway (Murthy et al, 1997) and prostaglandins (PGs) produced by the cyclooxygenases COX-1 or COX-2, are lipid mediators implicated in the pathophysiology of UC (Funk, 2001).

Inflammation in experimentally induced colitis is characterized by increased PGs such as PGE_2 and PGD_2. PGD_2 (Ajuebor et al, 2000; Melgar et al, 2006) is further converted by dehydratation to 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15d- PGJ_2) (Monneret et al, 2002), a stable PG and putative endogenous PPARγ ligand with cytoprotective and anti-inflammatory properties, and hence a new potential therapeutic target in inflammatory bowel diseases (Dubuquoy et al, 2006).

7α-Hydroxy-DHEA, the innate metabolite of dehydroepiandrosterone (DHEA), is normally produced in the colon and many other tissues (Doostzadeh & Morfin, 1996; Morfin & Courchay, 1994) but overproduced by IL-1β during the inflammatory process as shown in mice and humans (Dulos et al, 2004; Dulos et al, 2005). We have previously shown that pre-treatment with DHEA and 7α-hydroxy-DHEA resulted in protective anti-oxidant effects in the colon of healthy and colitis rats (Pelissier et al, 2004; Pelissier et al, 2006). 7α-Hydroxy-DHEA is converted by NADP(H)-dependent 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) to 7β-hydroxy-DHEA through an oxido-reductive process via 7-oxo-DHEA (Muller et al, 2006b). Through this mechanism, 7α-hydroxy-DHEA may inhibit 11β-HSD1-dependent production of inactive cortisone from active cortisol (Hennebert et al, 2007a).

Epiandrosterone (EpiA), which is derived from DHEA, is also converted into 7-hydroxylated metabolites (Kim et al, 2004). We have recently shown that 11β-HSD1 is responsible for converting 7α-hydroxy-EpiA into 7β-hydroxy-EpiA (Chalbot & Morfin, 2005; Hennebert et al, 2007b), which is readily produced in small quantities in human tissues (Jacolot et al, 1981; Kim et al, 2004).

7β-Hydroxy-EpiA has been shown to exert neuroprotective effects *in vivo* at remarkably low doses in animal models of cerebral ischemia (Pringle et al, 2003) and Alzheimer's disease (Dudas et al, 2004). However, dose levels needed to demonstrate these effects are far below the concentrations necessary to inhibit the 11β-HSD1-dependent-cortisol transformation indicating that other mechanisms may be involved.

Finally, studies in rheumatoid arthritis and brain injury models have shown that DHEA can modulate the expression of COX-2 mRNA or PGE_2 synthesis (Malik et al, 2003; Sun et al, 2006).

Taken together, these finding suggest that certain 7-hydroxysteroids may play a role in the modulation of PGs production in inflammation. This role may permit to resolve inflammation in inflammatory bowel diseases.

2. The resolution of inflammation

Inflammatory resolution occurs after the sharp PGE_2-driven inflammation process and is thought to result from cytoprotective PGD_2 and 15d-PGJ_2 action. A shift from arachidonic acid-derived PGE_2 to PGD_2 production occurs to these ends (Haworth & Buckley, 2007; Rajakariar et al, 2007) and is illustrated in Figure 1.

Figure 1 outlines the native inflammation process and its relations to immunity onset and circulating steroid metabolism. Inflammation-triggered increase in cellular cytochrome P450-7B1 which results in augmented 7α-hydroxy-steroid production was shown both in a
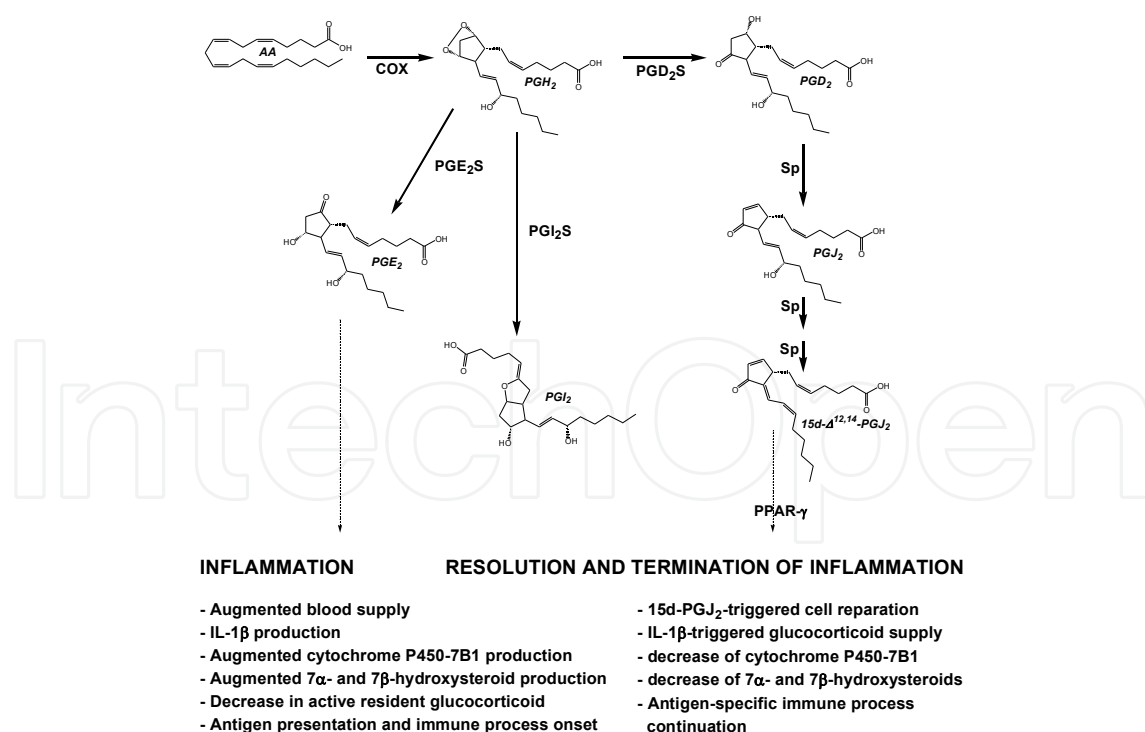

INFLAMMATION

- Augmented blood supply
- IL-1β production
- Augmented cytochrome P450-7B1 production
- Augmented 7α- and 7β-hydroxysteroid production
- Decrease in active resident glucocorticoid
- Antigen presentation and immune process onset

RESOLUTION AND TERMINATION OF INFLAMMATION

- 15d-PGJ_2-triggered cell reparation
- IL-1β-triggered glucocorticoid supply
- decrease of cytochrome P450-7B1
- decrease of 7α- and 7β-hydroxysteroids
- Antigen-specific immune process continuation

Fig. 1. At the onset of inflammatory response, arachidonic acid (AA) is converted to PGH_2 via COX. In turn, PGE_2, PGI_2 and PGD_2 are produced from PGH_2 by synthases (PGE_2S, PGI_2S, PGD_2S). PGD_2 is transformed non-enzymatically (Sp) to 15d-PGJ_2 which interacts with PPAR-γ. Non PPAR-γ-mediated action of 15d-PGJ_2 are not shown.

mouse model of rheumatoid arthritis and in humans with rheumatoid arthritis (Dulos et al, 2004; Dulos et al, 2005). Due to this increase, competitive inhibition of the cellular 11β-HSD1 may occur (Muller et al, 2006a) through use of the enzyme for transformation of 7α-hydroxysteroid into 7β-hydroxysteroids (Hennebert et al, 2007a; Muller et al, 2006b). Thus, the circulating inactive cortisone made available to the inflamed cells is not activated into cortisol which would quench the onset of immune processes. Our finding of a 7α-hydroxy-dehydroepiandrosterone-triggered increase of immune response in mice supports this relation to immunity onset (Morfin & Courchay, 1994).

These basic facts led to questions relative to the effect of 7β-hydroxysteroids on inflammation, PG metabolism, cell protection and related mechanisms of action. Answers were found through investigations using several models of inflammation in rats and humans.

3. Choice in the 7β-Hydroxysteroid used in treatments

Among 7β-hydroxysteroids, 7β-hydroxy-epiandrosterone (7β-hydroxy-EpiA) was selected because of its reported effects as a neuroprotector (Pringle et al, 2003). 7β-Hydroxy-EpiA is a native steroid which derives from testosterone and dehydroepiandrosterone as reported (Niro et al, 2010) and illustrated in Figure 2. The chemical synthesis of 7β-hydroxy-EpiA was carried out (Ricco et al, 2011) and provided 400 mg of the steroid which is available now for investigations in our group and abroad. Several doses of 7β-hydroxy-EpiA (0.01, 0.1 and 1 mg/kg) were used for the treatments.
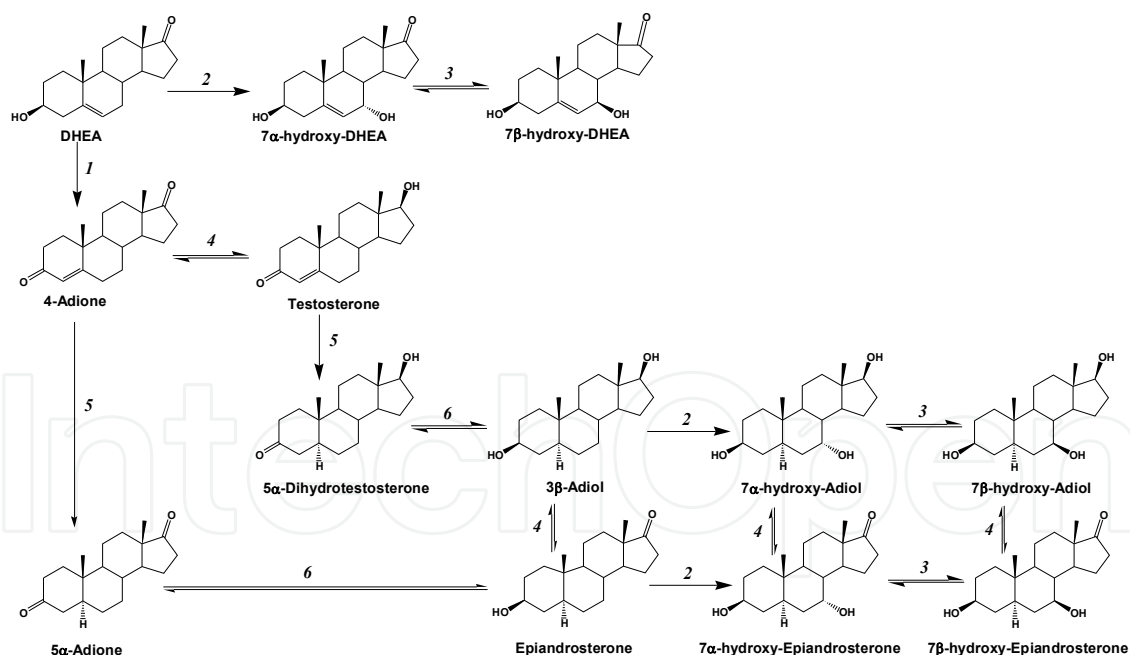

Fig. 2. Epiandrosterone derives from testosterone and dehydroepiandrosterone (DHEA) and is a substrate for cytochrome P450-7B1 (**2** EC 1.14.13.100) producing 7α-hydroxy-epiandrosterone which is inter-converted then into 7β-hydroxy-epiandrosterone by 11β-hydroxysteroid dehydrogenase type 1 (**3** EC 1.1.1.148). Other enzymes are **1**. 3β-hydroxy-5-ene steroid dehydrogenase (EC 1.1.1.145, EC 5.3.3.1) **4.** 17β-hydroxysteroid dehydrogenase (EC 1.1.1.51) **5.** Steroid Δ4-5α-reductase (EC 1.3.99.5) **6.** 3β-hydroxysteroid dehydrogenase (EC 1.1.1.51).

4. Investigations in rats with dextran sodium sulphate-induced colitis

4.1 Colitis induction and experimental design

Male Wistar rats (180-200g) were acclimated for 7 days and were divided into 2 controls groups (one sham-treated and one treated) and 2 colitis groups (one sham-treated and one treated). Treatments with 7β-hydroxy-EpiA were carried out for 7 days prior to colitis induction (Figure 3). Doses (0.01, 0.1 and 1 mg/kg) were dissolved in dimethyl sulfoxide and injected *i.p.* daily for 7 days. Dimethyl sulfoxide alone was injected to the sham-treated animals. Colitis was then induced by addition of 5% dextran sodium sulphate (DSS) to drinking water for 7 days. Plain water was given to the control groups. Clinical and histological signs of colitis occurred in all the DSS-treated rats. Typically, all the rats exhibited symptoms of colitis and severe diarrhea 5 days after the onset of DSS treatment followed by rectal bleeding and shortening of the colon after 7 days. Increase in colonic myeloperoxidase activity indicated an invasion of the colonic mucosa by neutrophils (Hennebert et al, 2008).
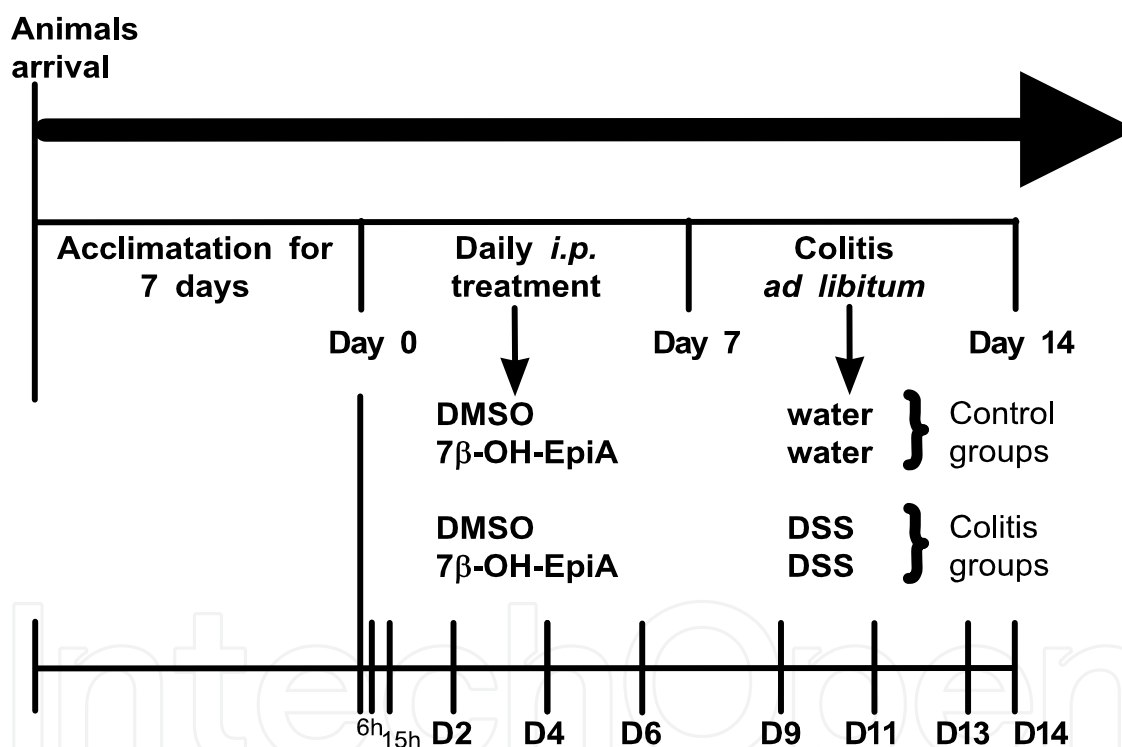

Fig. 3. Experimental design. DSS: 5% DSS in drinking water; DMSO: dimethyl sufoxide; 7β-OH-EpiA: 7β-hydroxy-EpiA in DMSO.

4.2 Histological examinations

A portion (1 cm) of the proximal colon was fixed in 4% formaldehyde and embedded in paraffin. Tissue sections (5 μm) were stained either with hematoxylin/eosin or Alcian blue for evaluation of colonic damage and mucus goblet cells content, respectively.

Major hallmarks of colonic inflammation, namely cryptic distorsion, neutrophil infiltration in the mucosal tissue (Figure 4B1), and loss of goblet cells which contained less mucins

(Figure 4B2) were apparent in the colitis group at day 13 and were more pronounced at day 14 (Figure 4D1-4D2) when compared with sham-control group (Figure 4A1,A2 and C1,C2).

The two low doses of 7β-hydroxy-EpiA (0.01, 0.1 mg/kg) prevented the DSS-induced colonic damages as indicated by the suppression of diarrhea and rectal bleeding. The colon length reduction was less pronounced in the groups treated by the low steroid doses (0.01, 0.1 mg/kg) than in the colitis group. All 7β-hydroxy-EpiA doses (0.01, 0.1 and 1 mg/kg) antagonized mucus depletion in goblet cells (Figure 4E2,F2,G2) and improved histological changes such as the abnormality of crypts and neutrophil infiltration (Figure 4E1,F1,G1) (Hennebert et al, 2008).
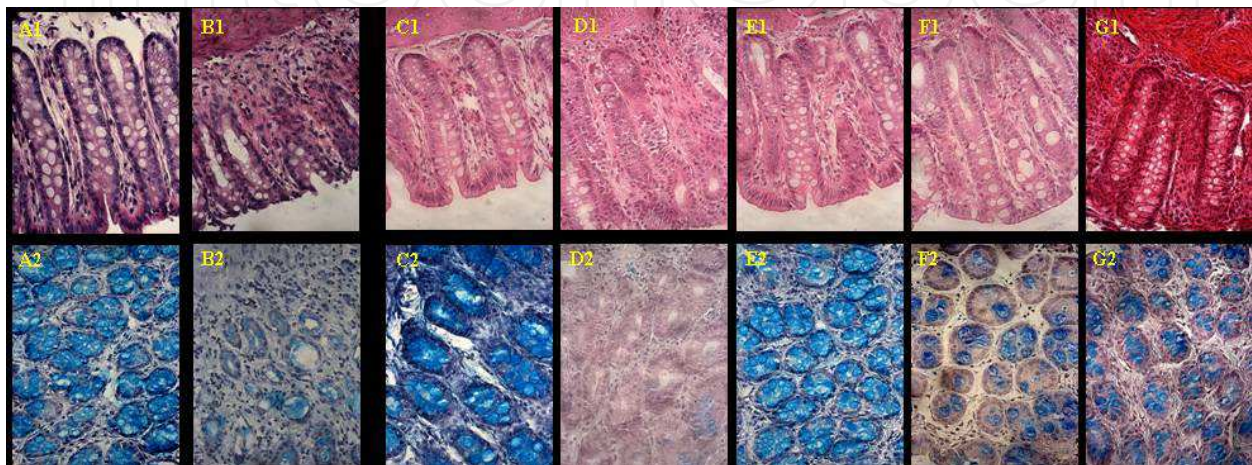

Fig. 4. Acute colitis induced by DSS: effect of 7β-hydroxy-EpiA on colon injury. Histological appearance of rat colonic mucosa after hematoxylin/eosin (A1-G1) or alcian blue stain (A2-G2) at days 13 and 14: sham (A1,A2) and DSS-treated (B1,B2) at day 13; sham (C1,C2) and DSS-treated (D1,D2) at day 14; and 0.01 mg/kg 7β-hydroxy-EpiA (E1,E2), 0.1 mg/kg (F1,F2) and 1 mg/kg (G1,G2) at day 14. No histological modification was present in sham animals (A and C) at days 13 and 14. Mucosal injury in DSS-induced colitis rats starting at day 13 and being more pronounced at day 14 (D) was characterized by necrosis of the epithelium, focal ulceration, infiltration of inflammatory cells and mucin goblet cell depletion. Treatment with 7β-hydroxy-EpiA (E-G) reduced the morphological alteration associated with DSS administration protecting the mucosal architecture. Magnification was 40x for all slices.

4.3 7β-Hydroxy-EpiA-induced changes in PG colonic tissue levels

7β-Hydroxy-EpiA treatments did not alter PGE_2 and PGD_2 colonic tissue levels in control rats without colitis (data not shown). DSS administration resulted into a marked increase of PGE_2, PGD_2 and 15d-PGJ_2 colonic synthesis at day 13 (Figure 5). At day 14, PGE_2 levels whereas PGD_2 synthesis was increased and 15d-PGJ_2 levels were reduced (Figure 5).

7β-Hydroxy-EpiA treatment in rats with DSS-induced colitis significantly decreased the colonic PGE_2 synthesis at days 13 and 14 when compared with untreated colitis rats. The greatest decrease was observed with the lowest dose (0.01 mg/kg) which led to a return towards basal values (Figure 5A). PGD_2 levels remained unchanged with the highest steroid-doses whereas the low doses (0.01 and 0.1mg/kg) caused a small but significant decrease (Figure 5B). Following the treatment with 7β-hydroxy-EpiA and throughout colitis

induction, 15d-PGJ$_2$ levels were maintained above control levels ranging from 5 to 14-fold increase (Figure 5C). Since 15d-PGJ$_2$ results from the produced PGD$_2$, addition of both PG levels may reflect the total production of PGD$_2$. This leads to observations identical with those derived from 15d-PGJ$_2$ measurements alone (Figure 4D). The decrease in 15d-PGJ$_2$ observed at the end of colitis induction underlies that 7β-hydroxy-EpiA treatment produced large amounts of 15d-PGJ$_2$ prior to colitis induction. This was confirmed after measurement of colonic 15d-PGJ$_2$ during 7β-hydroxy-EpiA treatment (Figure 5). Thus, a 51-fold increase was obtained with the 0.1 mg/kg dose at day 2 (D2) and decreased progressively from D4 to D6 (increments ranging from of 44-fold to 5-fold) (Figures 5C and 6). Conclusion of these findings is that 7β-hydroxy-EpiA treatments induced a shift from PGE$_2$ to 15d-PGJ$_2$ production (Hennebert et al, 2008).
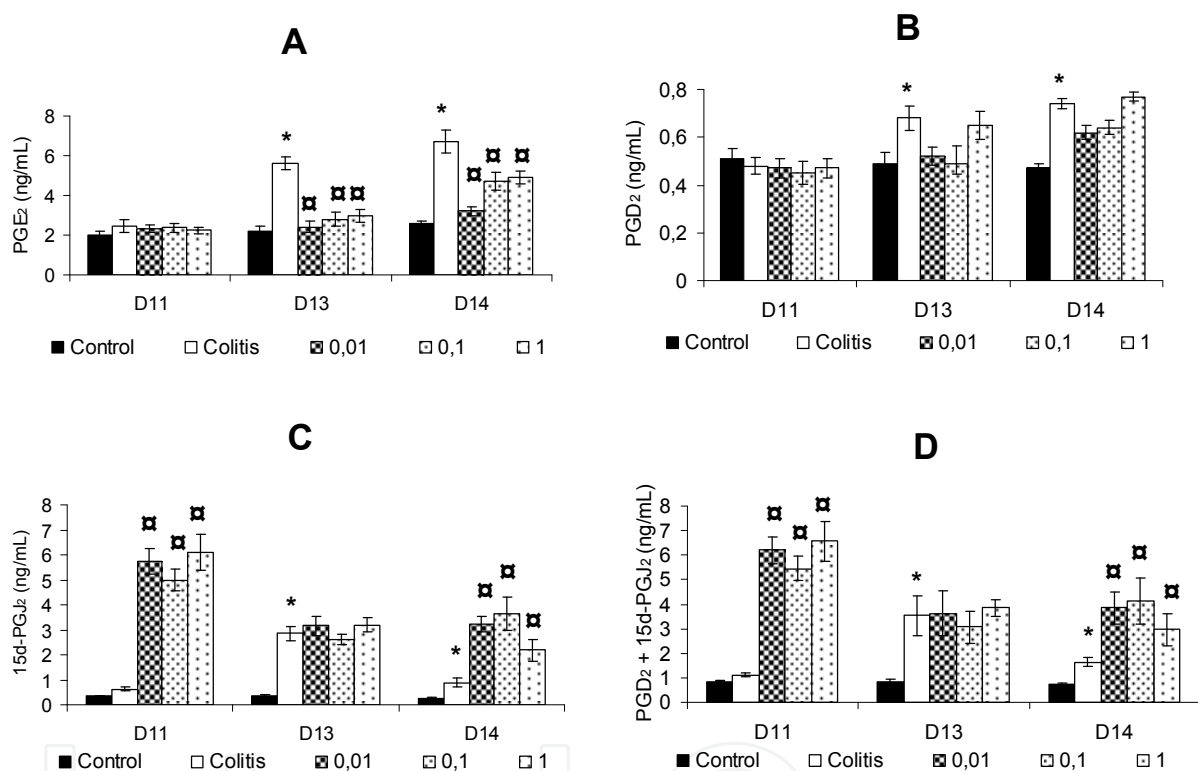

Fig. 5. Effect of 7β-hydroxy-EpiA on colonic synthesis of PGE2 (A), PGD2 (B), 15d-PGJ2 (C) and PGD2+15d-PGJ2 (D). Measurements were carried out in triplicate during DSS administration at days D11, D13 and D14. Data are expressed as mean ± S.E.M. with n=3-15 (*) Dextran sodium sulphate-induced colitis group versus Sham-control group; (¤) 7β-hydroxy-EpiA treated group versus Dextran sodium sulphate-induced colitis group ($p <$ 0.05).

4.4 7β-Hydroxy-EpiA-induced changes in PG-producing enzymes

Because significant modifications in prostaglandin levels were observed with DSS administration and 7β-hydroxy-EpiA treatments, we tested whether the expression of COX-2, mPGES-1 and H-PGDS was altered by quantifying specific mRNA by real-time RT-PCR. Transcription of these genes was examined and related to that of the HPRT1 house-keeping gene (Hennebert et al, 2008).
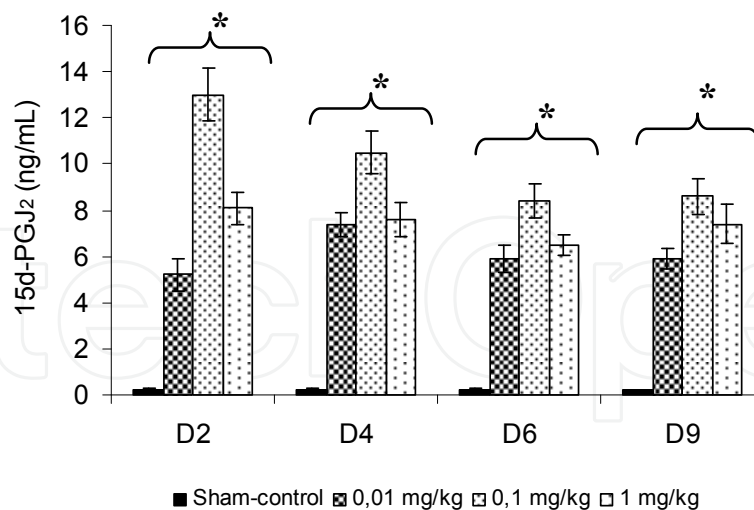
Fig. 6. Colonic 15d-PGJ2 levels at various times during and after 7β-hydroxy-EpiA treatment (D2-D9). Values are mean ± S.E.M. (n= 3-15) . (*) comparison to the sham-control group (*p*<0.05).

In control rats without colitis, the daily 7β-hydroxy-EpiA treatment (0.1 mg/kg) induced a significant 1.5 fold increase in COX-2 mRNA levels at 15h followed by a decrease up to day 4 and thereafter returned to basal values (Figure 7A). mPGES-1 mRNA expression increased transiently between 6h to 15h returning towards basal levels at day 2. H-PGDS mRNA expression remained similar to that in sham-control rats throughout the time course.

After colitis induction, a 2.5 fold increase in COX-2 mRNA expression was observed at days 13 and 14 of DSS administration (Figure 7B) while mPGES-1 mRNA was significantly augmented at day 13 only (Figure 7C). H-PGDS was not altered by colitis (Figure 7D). In conclusion, 7β-hydroxy-EpiA treatment (all doses) suppressed the increase in both COX-2 and mPGES-1 mRNA synthesis in the colitis group from day 13 to day 14 (Figure 7).

4.5 7β-Hydroxy-EpiA overall effects on colitis

Colitis was fully induced in untreated rats after DSS administration for 7 days. Treatment for 7 days with several doses of 7β-hydroxy-EpiA prior to colitis induction led to a prevention of colitis onset. Examination of myeloperoxidase activity and oxidative stress markers such as carbonylated proteins and Tbars provided evidence of their decrease after steroid treatment (Hennebert et al, 2008). The preventive effects of 7β-hydroxy-EpiA could result in part from the early increase of the prostaglandin 15d-PGJ$_2$ that might contribute to down regulate the inflammatory response. 7β-Hydroxy-EpiA triggered an increase in COX-2 and m-PGES1 expression but depressed the elevation of colonic PGE$_2$ synthesis in dextran sodium sulphate-treated rats. Thus, 7β-hydroxy-EpiA triggered a shift from the PGE pathway towards the PGD pathway, causing increased production of 15d-PGJ$_2$, the dehydrated stable metabolite of PGD$_2$ (Scher & Pillinger, 2005). Our finding that small doses of 7β-hydroxy-EpiA, an endogenous steroid produced in colon, can prevent colonic damage through a shift from PGE$_2$ to PGD$_2$ production via changes in COX-2 expression, followed by an increase of 15d-PGJ$_2$ levels in the colon result from investigations carried out on a rat
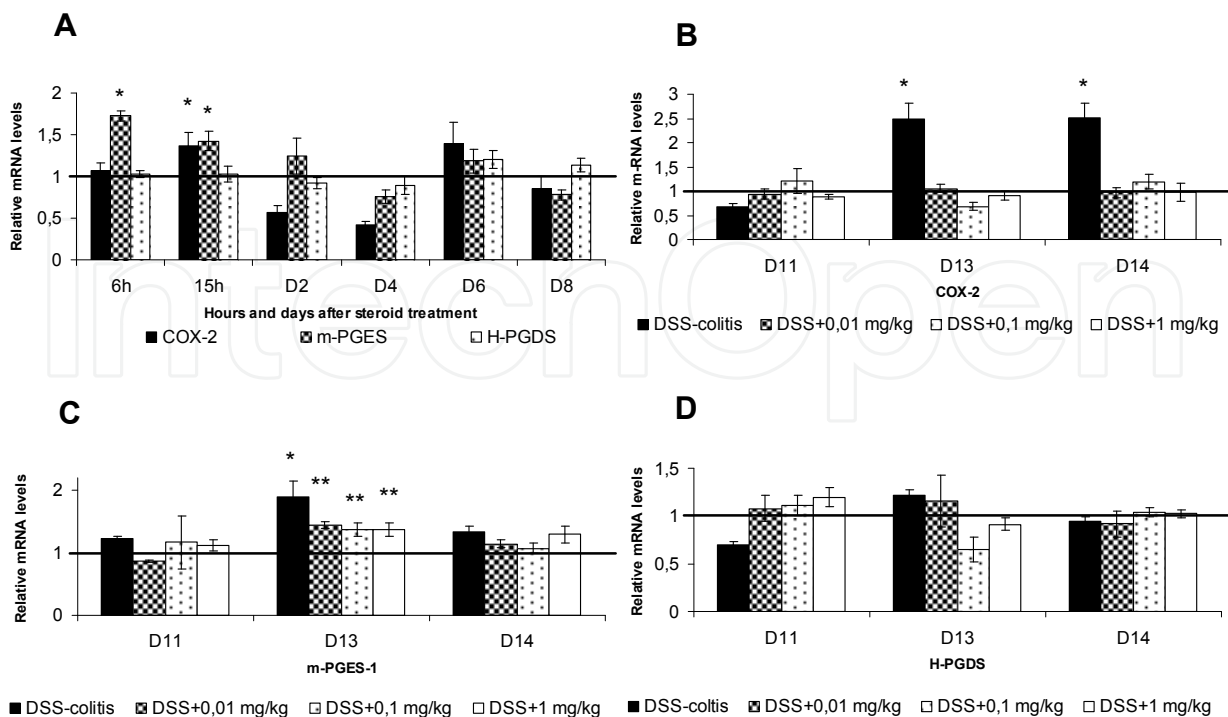
Fig. 7. Colonic expression of COX-2, m-PGES1 and H-PGDS mRNA after 0.1 mg/kg 7β-hydroxy-EpiA treatment and before colitis induction (A). During colitis induction, mRNA levels for COX-2 (B), m-PGES-1 (C) and H-PGDS (C) were measured at days 11, 13 and 14. mRNA levels are expressed relative to that of HPRT1 standing at a basal level of 1 shown as a continuous line. (*) DSS-colitis versus basal level ($p < 0.05$). (**) DSS + 0.01, 0.1 and 1 mg/kg 7β-hydroxy-EpiA-treated group versus DSS-colitis group ($p < 0.05$).

model where inflammation and colitis were obtained by dextran sodium sulphate administration. Two immediate questions arise from these findings: i) does this process, leading to the resolution of inflammation, occur in any inflammation? ii) is 7β-hydroxy-EpiA as efficient in humans as in rats when faced with inflammation? Answers to these questions were seek in human cell cultures.

5. A model for inflammation studies in humans

Addition of TNF-α to cultures of human peripheral blood monocytes (PBMC) results into the cellular stress found in inflammatory conditions through production of mediators released from the eicosanoid pathway. These mediators include PGE_2 that is associated with inflammation, and PGD_2 and 15d-PGJ_2 which are associated with the resolution of inflammation (Haworth & Buckley, 2007). Therefore, we used human PBMC cultured in the presence or absence of 0.01 µg/mL TNF-α in order to test the effects of 7β-hydroxy-EpiA on PG production (Le Mee et al, 2008). PBMC were cultivated either for 4 or 24 hours. RIA measurements were carried out for the PG levels released in the medium, and mRNA of the eicosanoid pathway were measured in cell extracts by quantitative PCR. All mRNA measurements were made relative to the expression of house-keeping gene HPRT1 (Le Mee et al, 2008).

5.1 7β-Hydroxy-EpiA-induced a shift in PG production

7β-Hydroxy-EpiA addition to the medium induced no significant change in PG levels in PBMC cultured for 4 h. In marked contrast, significantly increased 15d-PGJ$_2$ levels were obtained after cultivation for 24 h (Figure 8). This increment occurred both in the presence and in the absence of TNF-α. A significant decrease in PGE$_2$ levels was also obtained in the presence of TNF-α only (Figure 8B). These findings indicated that 7β-hydroxy-EpiA treatment of TNF-α-associated inflammation patterns were causative of a shift from PGE$_2$ to 15d-PGJ$_2$ production. Since 15d-PGJ$_2$ is a spontaneous dehydrated derivative of PGD$_2$, production of PGD$_2$ must have been increased along with the inflammation-related conditions for its conversion to 15d-PGJ$_2$ (Le Mee et al, 2008). 7β-Hydroxy-EpiA-triggered changes in the expression of the enzymes producing PGE$_2$ and PGD$_2$ had to be examined then.
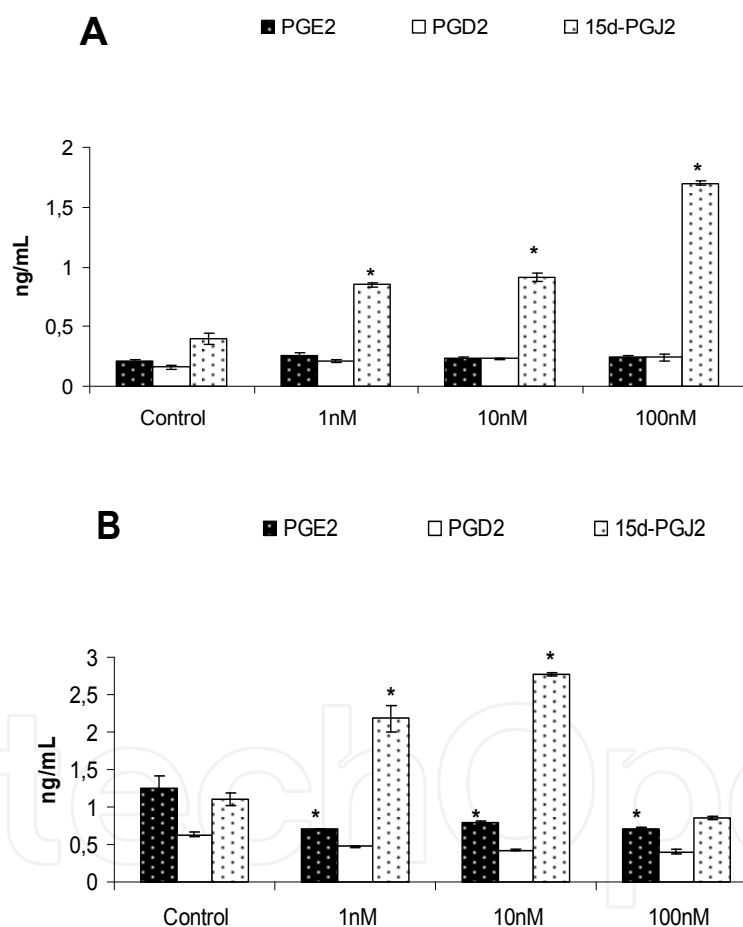

Fig. 8. PG levels released in the medium of human PBMC cultured for 24 h fortified with 1-100 nM 7β-hydroxy-EpiA. Cultures were carried out in the absence (A) or in the presence of TNF-α (B). (*) significantly different from controls ($p < 0.05$).

5.2 7β-Hydroxy-EpiA-induced changes in eicosanoid pathway enzyme expression

In addition to COX-2 and m-PGES1 which are responsible for arachidonic acid conversion to PGH2 and PGE2, respectively, we measured the mRNA levels of the known two enzymes

responsible for PGD2 production, namely H-PGDS and L-PGDS. No significant change in enzyme mRNA levels was found in cells culture with 7β-hydroxy-EpiA for 4 h. In marked contrast, cultivation for 24 h led to significant differences in enzyme expression. Cultures without addition of TNF-α showed that 7β-hydroxy-EpiA significantly increased m-PGES1 and decreased H-PGDS mRNA levels (Figure 9A). The findings were opposite in the presence of TNF-α, with significant decrease in m-PGES1 and no change in H-PGDS mRNA levels (Figure 9B). No significant effect of 7β-hydroxy-EpiA was found for COX-2 and L-PGDS. These findings parallel well with PG levels measurements, and imply that the 7β-hydroxy-EpiA-triggered shift from PGE_2 to 15d-PGJ_2 production is mainly due to a lower expression of the m-PGES1 enzyme responsible for PGE2 production (Le Mee et al, 2008).
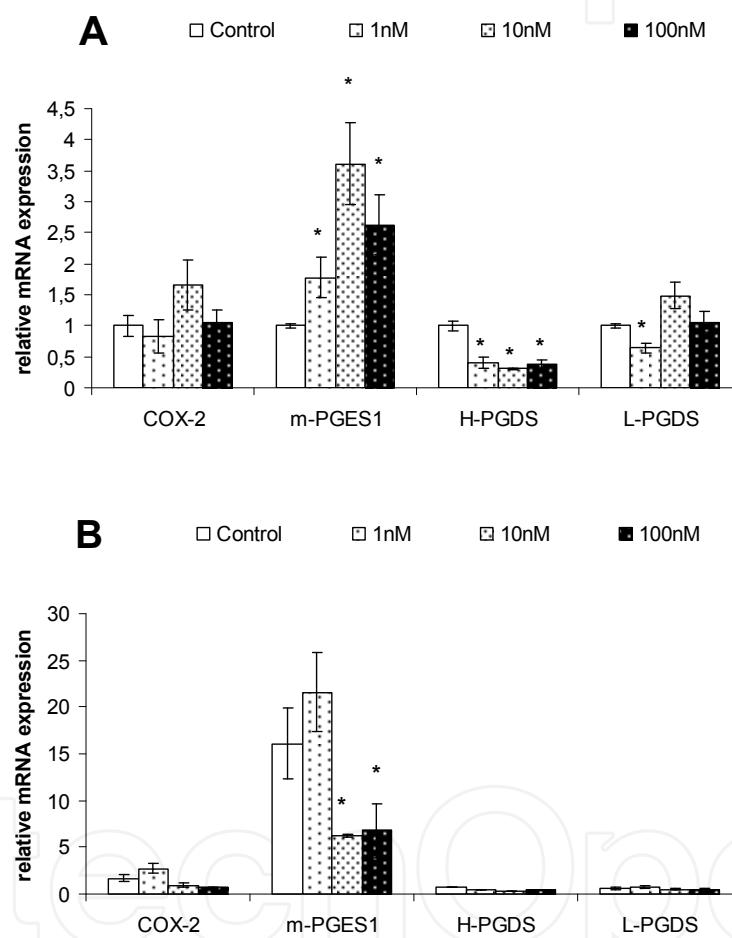

Fig. 9. Measurement of COX-2, m-PGES1, H-PGDS and L-PGDS mRNA levels relative to the expression of house-keeping gene HPRT1. The human PBMC were cultured for 24 h without or with 1-100 nM 7β-hydroxy-EpiA. Cultures were carried out in the absence (A) or the presence of TNF-α. (*) significantly different from control group ($p < 0.05$).

5.3 A putative specific receptor for 7β-Hydroxy-EpiA

Our findings that a 10^{-9} M dose of 7β-hydroxy-EpiA was a trigger for the resolution of inflammation and for cellular protection led us to consider this steroid as a possible candidate for interference with a putative nuclear receptor. A precursor for 7β-hydroxy-

EpiA, namely 5α-androstane-3β,17β-diol, was shown to bind preferentially to the estrogen receptor-β (ER-β) with agonistic activity and a K_d of 2 nM (20 times larger than for estradiol) (Kuiper et al, 1997). Several reports inferred that ER-β was involved in the protection against breast and prostate cancer (Dondi et al, 2010; Nilsson et al, 2001), and this led us to test this hypothesis on three breast cancer cell lines, namely, MCF-7, MDA-231 and SKBR-3 (Niro et al, 2011).

6. Tamoxifen-like effect of 7β-Hydroxy-EpiA on breast cancer cell proliferation

Among ERs, MCF-7 cells are known to express ER-α, ER-β and GPR30. MCF-7 cells proliferate in the presence of 10^{-8} M estradiol, and their proliferation is markedly inhibited by 10^{-6} M tamoxifen (TAM), even in the presence of estradiol. Cultivations in the presence of 10^{-7}-10^{-9} M 7β-hydroxy-EpiA without TAM or estradiol inhibited MCF-7 cell proliferation to TAM levels, whereas use of both TAM and 7β-hydroxy-EpiA, or estradiol + 7β-hydroxy-EpiA, decreased the proliferation below TAM levels (Figure 10A). These results indicated that 7β-hydroxy-EpiA doses 10-10^3 lower than the TAM dose produced TAM-like effects on MCF-7 growth. In contrast, the MDA-231 cell receptor status is ER-β+, GPR30+. Their proliferation was not increased by estradiol, and TAM effects were not as strikingly important as in MCF-7 cells (Niro et al, 2011).

Cultivations of the MDA-231 cells in the presence of 10^{-7}-10^{-9} M 7β-hydroxy-EpiA without TAM or estradiol did not significantly change the proliferation patterns, whereas use of either estradiol + TAM or estradiol + 7β-hydroxy-EpiA, decreased the proliferation much below TAM or estradiol levels (Figure 10B). In the case of SKBR-3 cells, le receptor status is GPR30+. SKBR-3 cell line proliferation was not significantly changed by estradiol, TAM or 10^{-7}-10^{-9} M 7β-hydroxy-EpiA. Cultivations of SKBR-3 cells in the presence of estradiol + 7β-hydroxy-EpiA significantly decreased cell proliferation (Figure 10C) (Niro et al, 2011).

The conclusions drawn from these studies imply the native 7β-hydroxy-EpiA in the regulation of ER-mediated estrogen effects. As for TAM, the responsiveness of MCF-7 cells to 7β-hydroxy-EpiA was better than for MDA-231 and SKBR-3 cells, and this implied that the antiproliferative and cytoprotective effects can be mediated by a receptor linked to one or several ERs. In any case, the receptor responsible for 7β-hydroxy-EpiA effects needs to be identified and whether and how ERs are involved in the mechanism leading to cell protection require further examination.

7. Pathophysiological significance of 7β-Hydroxy-EpiA levels

The first requirement for the production of native 7β-hydroxy-EpiA is the presence of the steroid hormone substrate testosterone for generation of epiandrosterone by the classical steroid metabolism (Figure 2). Scarce studies were addressed to the levels of circulating epiandrosterone in humans. This may be due to ignorance of its fate in hormonal and physiological processes. Two key enzymes are required then for 7β-hydroxy-EpiA production. One is CYP7B1 which provides a hydroxyl at the 7α- position on epiandrosterone, and the second is 11β-HSD1 which converts 7α-hydroxy-EpiA into 7β-hydroxy-EpiA. Both enzymes
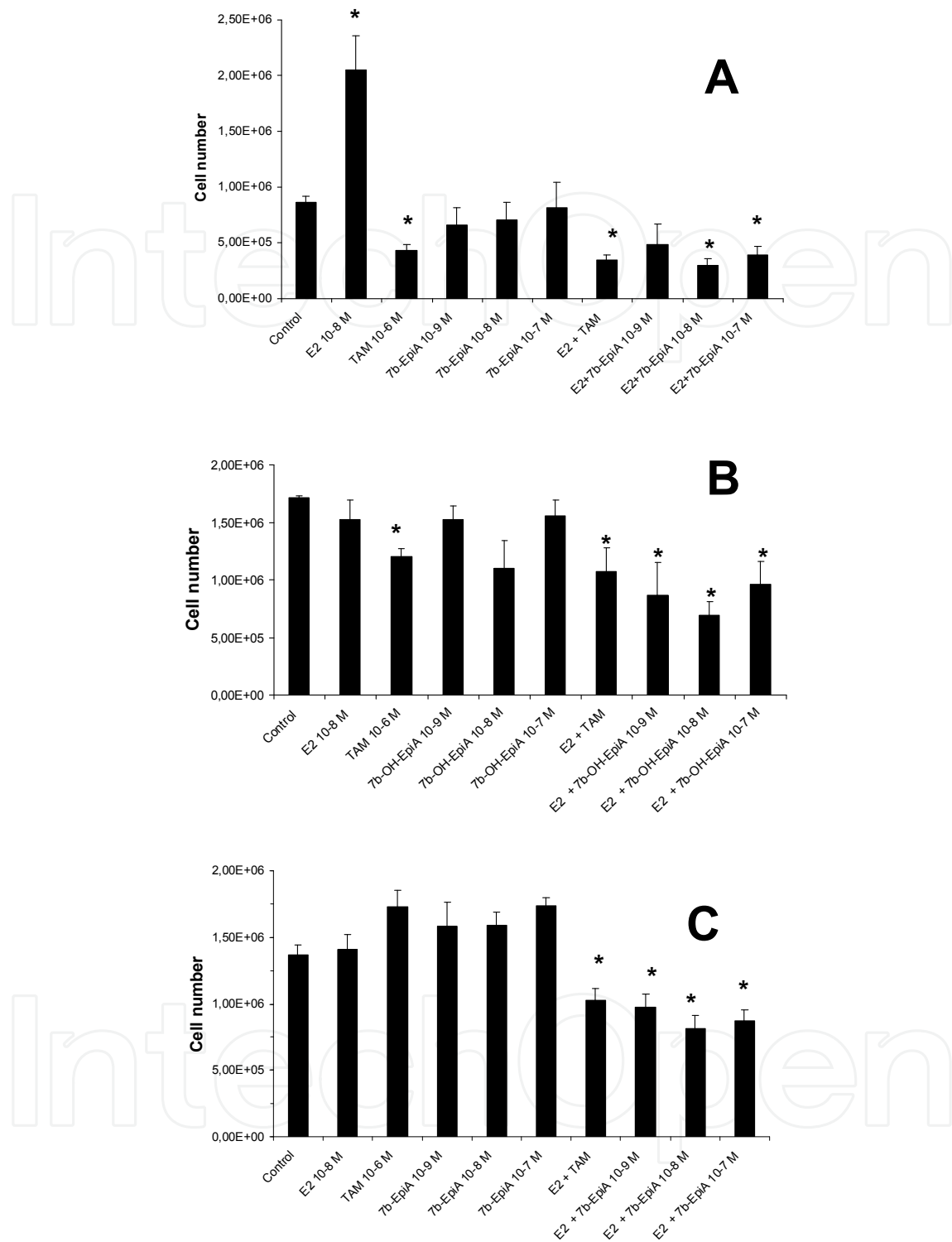
Fig. 10. Tamoxifen-like effects of 7β-hydroxy-EpiA on the proliferation of MCF-7 (A), MDA-231 (B) and SKBR-3 cell lines. Cells (10^5) were seeded in triplicate in 24-well plates, and adherent cells were cultivated in 1 mL growth medium at 37°C, 95% humidity and in the presence of 5% CO_2 for 72h. Estradiol (E2), 7β-hydroxy-EpiA (7β-EpiA) and tamoxifen (TAM) were administered in 5µL ethanol at the beginning of assays. Controls contained 5µL ethanol only. * Indicates a significant difference with controls ($p < 0.05$).

are ubiquitous in human tissues, and any deficit in their expression may lead to related pathologies. Their outcome may also be related to aging since the production and levels of steroid precursors such as DHEA and testosterone are known to be significantly decreased after the fifth decade in humans. These considerations would be strongly supported by precise measurements of the 7β-hydroxy-EpiA circulating levels in humans.

Finally, variations in the susceptibility for the development of diseases may depend on 7β-hydroxy-EpiA receptor availability and function (Nilsson & Gustafsson, 2002). The precise mechanism of action and the Ers involvement are to be deciphered in order to give a full support to 7β-hydroxy-EpiA beneficial effects.

8. Concluding remarks

DHEA and testosterone-derived metabolites, namely epiandrosterone and 5α-androstane-3β,17β-diol, are substrates for the CYP7B1 and their 7α-hydroxylated products are also converted into 7β epimer by the 11β-HSD1. When assayed in rat colitis and inflamed human PBMC at doses 10^4 lower than circulating free DHEA or testosterone, 7β-hydroxy-EpiA was shown to shift the PG metabolism from PGE_2 to 15d-PGJ_2 production, thus triggering the resolution of inflammation. In addition, 7β-hydroxy-EpiA (1 nM) exerted the same effects as TAM (1 µM) on the proliferation of MCF-7, MDA-231 and SKBR-3 human beast cancer cell lines. These findings suggest that the observed effects of 7β-hydroxy-EpiA could be mediated in part by ERs.

This overview of recent studies implies that DHEA and/or testosterone are precursors for 7β-hydroxy-EpiA acting on inflamed tissues for the resolution of inflammation through a putative receptor. CYP7B1 and 11β-HSD1 are two key enzymes involved in 7β-hydroxy-EpiA production, and their expression in colitis and other inflammatory diseases could be a rewarding target in further studies.

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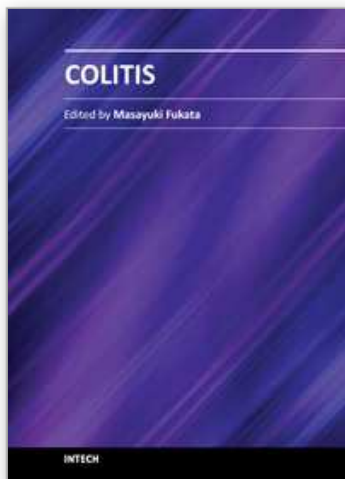
Colitis

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Inflammation of the colon is collectively called "Colitis". Since a variety of conditions may cause colitis and its manifestations are similar among the causes, selection of the right treatment based on the correct diagnosis is important in the management of this group of illnesses. Over the last few decades, a major shift has been observed in the clinical attention to the pathogenesis of colitis from infectious to idiopathic inflammatory bowel diseases. Colitis cases that are associated with chemical therapeutics and specific pathogens such as amoeba, have become prominent in hospitalized individuals and immune deficient patients, respectively. In addition, a great deal of progress has been made in colitis research triggering the need for updating our knowledge about colitis. This book Colitis provides comprehensive information on the pathogenesis, mechanism of resolution, and treatment strategies of colitis.

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