Up-regulation of cyclooxygenase-1 in neuroblastoma cell lines by retinoic acid and corticosteroids

Norbert Schneider,* Stefan Lanz,* Robert Ramer,* Dirk Schaefer† and Margarete Goppelt-Struebe*

*Medizinische Klinik IV, Universität Erlangen-Nürnberg, Erlangen, Germany
†Kompetenzzentrum Umweltmedizin, Ruprecht-Karls-Universität Heidelberg, Mannheim, Germany

Abstract
Cyclooxygenases-1 and -2 are both expressed in neuronal cells in vivo. In the neuroblastoma cell lines NG108 and N2a, however, only cyclooxygenase-1 was detectable. Differentiation of the cells with retinoic acid increased cyclooxygenase-1 mRNA and protein expression within 24 and 48 h, respectively. A further increase was observed when the cells were concomitantly treated with the glucocorticoid dexamethasone (a 2–3-fold increase compared with retinoic acid alone). In the absence of retinoic acid, dexamethasone only slightly up-regulated cyclooxygenase-1 expression. The inhibitor of protein synthesis cycloheximide abrogated the effect of dexamethasone, indicating the involvement of newly synthesized proteins. Retinoic acid increased the transcription of cyclooxygenase-1 mRNA, determined with a luciferase-coupled promoter construct. Dexamethasone only slightly augmented cyclooxygenase-1-promoter activity but increased cyclooxygenase-1 mRNA stability. Other corticosteroids, hydrocortisone and aldosterone, also up-regulated cyclooxygenase-1 whereas neurosteroids or oestrogen were ineffective. Up-regulation was mediated primarily by the glucocorticoid receptor, because the receptor antagonist RU486 strongly reduced the effects of all corticosteroids. This indicated that in NG108 cells, the mineralocorticoid aldosterone may bind to the glucocorticoid receptor. Treatment of NG108 or N2a cells with corticosteroids did not alter the morphological phenotype obtained during differentiation. We thus show that corticosteroids, which down-regulate cyclooxygenase expression in most cell types, up-regulate cyclooxygenase-1 during neuronal differentiation.


In the nervous system, prostanoids are involved in the regulation of cerebral blood flow and the sleep/wake cycle, modulation of pain responses and the hypothalamic control of the stress response (O’Banion 1999). Cyclooxygenases, Cox-1 and Cox-2, are key regulators of prostanoid synthesis. Both isoforms have been described in neuronal cells. In contrast to many other organs, Cox-2 is the predominant isoform in the brain and has been associated with various types of cortical but also subcortical neurones (Kaufmann et al. 1997; O’Banion 1999). In rat cerebral cortex, it has been localized to excitatory neurones and seems to be involved in synaptic transmission (Kaufmann et al. 1996). In rats, neuronal Cox-2 expression is induced by seizures, global ischemia or experimental trauma (summarized in O’Banion 1999). Much less is known about the expression and function of Cox-1 in neuronal cells. Cyclooxygenase-1 was mapped in the ovine brain and observed in areas involved in complex integrative processes and central autonomic regulation (Breder et al. 1992). In the human brain, Cox-1 immuno-reactivity has recently been localized to hippocampal neurones, certain neurones of the neocortex and some pyramidal neurones (Yermakova et al. 1999). Cyclooxygenase-1 levels are modulated during development. Cyclooxygenase-1 mRNA expression was barely detectable in brains of fetal rats and increased during development...
reaching the highest levels in adult animals (Kawasaki et al. 1993). Similar developmental changes were observed in pigs, where twofold higher Cox-1 levels were detectable in juvenile brain tissue compared with new-borns (Peri et al. 1995). In ovine fetal brain, Cox-1 was associated with the control of breathing activity (Norton et al. 1996). All these changes seem to relate to modulation of physiological responses.

Regulation of Cox-1 and Cox-2 expression has been studied in many in vitro systems (Goppel-Streube 1995; Herschman 1996). In most instances, Cox-2 was found to be regulated by a whole variety of stimuli, whereas Cox-1 behaved as a house-keeping gene, which are constitutively expressed in most cell types. Rather little is known about the regulation of Cox isoforms in neuronal cells from in vitro studies. Using transfected mouse and human neuroblastoma cells Bazan et al. described the induction of Cox-2 promoter constructs by platelet-activating factor and retinoic acid (Bazan et al. 1994). However, no data on the regulation of the endogenous cellular Cox-2 were presented. Rather unexpectedly, up-regulation of Cox-1 was detected in the endogenous cellular Cox-2 were presented. Rather

Based on these data, it was the aim of this study to investigate the expression and regulation of Cox-1 and -2 in neuroblastoma cells. NG108 and neuro2a (N2a) neuroblastoma cells were differentiated with retinoic acid and, in addition, were co-incubated with corticosteroids, dexamethasone, aldosterone and hydrocortisone.

**Materials and methods**

**Materials**

Murine neuro2a (N2a) cells were obtained from the American Type Culture Collection (Rockville, MD, USA). NG108 cells (mouse neuroblastoma – rat glioma hybrid cell line) were kindly provided by Drs H. Ammer and R. Schulz (University of Munich, Germany). 5,6-Dichloro-1-β-D-ribofuranosylbenzimidazole (DRB) and dibutyryl cAMP were obtained from Calbiochem (Bad Soden, Germany). Retinoic acid, dexamethasone, aldosterone, RU486, hydrocortisone, estradiol, dibydroepiandrosterone, dibydroepiandrosterone sulfate, isophorone A23187, 12-O-tetradecanoylphorbol-13-acetate and cycloheximide were obtained from Sigma (Deisenhofen, Germany). Stock solutions of retinoic acid and steroids were prepared in DMSO and ethanol, respectively. Appropriate solvent controls were performed throughout the studies.

**Cell culture**

NG108 cells were cultured in Dulbecco’s modified Eagle’s medium (DMEM) with 10% fetal calf serum (FCS), 2% HAT supplement (10 mM hypoxanthine, 40 mM aminopterin, 1.6 mM thymidine; Gibco/Life Technologies, Eggenstein, Germany), 2 mM L-glutamine, 4.5 g/L glucose, 100 U/mL penicillin and 100 µg/mL streptomycin. For the experiments the cells were seeded at a density of 1.3 × 10^6 cells/mL in 10-cm diameter Petri dishes in medium supplemented with 10% FCS. After an overnight culture the cells were cultured further in medium with 1% FCS in the presence or absence of retinoic acid and steroids. In some experiments, the cells were seeded directly in medium with a low concentration of serum.

Neuro2a cells were cultured in DMEM with 10% FCS, 2 mM t-glutamine, 1.0 g/L glucose, 100 U/mL penicillin and 100 µg/mL streptomycin. Cells were seeded at a density of 0.8 × 10^6 cells in medium with 10% FCS. After an overnight culture the cells were differentiated with retinoic acid in medium with 2% FCS.

**Northern blot analysis**

Northern blot analysis was performed essentially as described previously (Stroebel and Goppel-Streube 1994). After stimulation for the indicated times, total RNA was extracted according to the protocol of Chomczynski and Sacchi (1987), with minor alterations. Usually, the RNA yield was about 30–40 µg in a Petri dish of 10-cm diameter. Separation of total RNA (20 µg/lane) was achieved by the use of 1.2% agarose gels containing 1.9% formaldehyde with 1x 3-[N-morpholino]propanesulfonic acid (MOPS) as gel running buffer. Separated RNA was transferred to nylon membranes (Biodyne A Transfer Membrane; Pall Biosupport Division, Dreieich, Germany) by capillary blotting and fixed by baking at 80°C for 2 h.

Hybridization was performed with cDNA probes labelled with [32P]deoxycytidine 5'-triphosphate (dCTP) using the Appligene NonaPrimer II kit (Appligene, Heidelberg, Germany). Specific Cox-1 and Cox-2 probes were 2.77-kb and 1.16-kb EcoRI fragments from the 5'-end of mouse cDNA (DeWitt and Meade 1993). Hybrids of DNA/RNA were detected by autoradiography using Kodak X-Omat AR (Deisenhofen, Germany) or Biomax film (Deisenhofen), or by phosphoimager analysis.

**Western blot analysis**

After stimulation, the cells were washed once with phosphate buffered saline (PBS) and then solubilized in 6 M guanidinium thiocyanate (6 M GTS)-buffer [6 M GTS containing 0.5% (w/v) deoxycholic acid and 0.1% (v/v) sodium dodecyl sulfate, 150 mM NaCl, 1 mM phenylmethylsulfonyl fluoride, 1 mM sodium vanadate and 14 µg/mL apro tinin]. Protein concentration was determined using the Bio-Rad protein assay. For western blot analysis, 30 µg protein were separated by sodium dodecyl sulfate – polyacrylamide gel electrophoresis (SDS–PAGE; 10% polyacrylamide), transferred onto polyvinylidene difluoride (PVDF) membrane (Pall Biosupport Division; Dreieich, Germany) and probed with specific antibodies. The antibody directed against Cox-1 was kindly provided by A. Habib (INSERM 348, Paris, France). Western blots were quantified by densitometry. To correct for equal loading, the gels were stained with Coomassie blue and a band with a molecular mass of about 50 kDa, which was not regulated, was scanned.

**Prostaglandin synthesis**

To determine Cox activity, the cells were treated with 10 µM arachidonic acid for 30 min. Supernatants were collected and determined prostaglandin E2 (PGE2) concentration by enzyme-linked immunosorbent assay (ELISA) as described by Schaefer et al. (1996). The monoclonal antibody used in the ELISA did not cross-react with arachidonic acid.
Transfection of NG108 cells

The luciferase reporter plasmid (pGL2-basic from Promega) containing a 2283-bp mouse Cox-1 promoter fragment was kindly provided by D. DeWitt (Michigan State University, MI, USA). For transient transfections, NG108 cells (1.5 × 10⁶ cells per 10 mL) were cultured in serum-containing medium overnight and then transfected with 10 μg DNA mixed with 60 μL Superfect® (Qiagen; Hilden, Germany) for 4 h according to the manufacturer’s instructions. After transfection, the cells were kept in fresh medium with 10% FCS overnight, then were combined and seeded into small Petri dishes with medium containing 1% FCS. Equal transfection efficiency was thus obtained in all samples. Stimulation time was 20 h.

Luciferase assay

Cyclooxygenase-1 promoter activity was determined by a luciferase assay. After stimulation, cells were washed with PBS, scraped in 1 mL PBS, pelleted and resuspended in 120 μL extraction buffer (pH 7.8, 15 mM K₂HPO₄, 120 mM KH₂PO₄, 1 mM DTT). The cells were lysed by four freeze-thaw cycles (liquid nitrogen/37°C, 2 min each). After centrifugation at 12 000 g, 4°C for 10 min, supernatants containing cellular proteins were collected and stored at −80°C until use. Fifty microlitres of supernatant were added to 100 μL luciferase buffer (pH 7.8, 15 mM K₂HPO₄, 120 mM KH₂PO₄, 15 mM MgSO₄, 5 mM ATP) and luciferase activity was measured in a Lumat LB 9501 luminometer (Berthold; Munich, Germany) with luciferin (100 μM, Roche Diagnostics; Mannheim, Germany) as substrate.

Results

Expression of Cox-1 during retinoic acid-induced differentiation

NG108 and N2a cells were differentiated by treatment with retinoic acid. During this time the cell morphology changed and the cells developed neurite outgrowths as described previously (Shea et al. 1985; Kozireski-Chuback et al. 1999).

Low levels of Cox-1 mRNA were detected in undifferentiated cells in both cell lines (Fig. 1a). Steady state levels of Cox-1 increased within 24 h when the cells were treated with retinoic acid (20 μM, Fig. 1a). Compared with untreated cells, retinoic acid enhanced Cox-1 mRNA expression about threefold in NG108 cells (Fig. 1b). Prolonged incubation with retinoic acid did not further enhance the level of Cox-1 mRNA (data not shown).

Cyclooxygenase-1 protein levels were only slightly increased after 24 h, but were substantially enhanced after 48 h in both cell lines (Fig. 1c).

The inducible isozyme Cox-2 was neither detectable in control cells nor in differentiated cells by northern or western blot analysis, nor was it detected after induction of apoptosis by serum deprivation. Dependent on the cell type, induction of Cox-2 is mediated by different intracellular signalling pathways (Goppelt-Struwe 1995). Activation of protein kinases C by phorbol ester, increased levels of
intracellular calcium, as well as activation of protein kinase A by elevated levels of cAMP may induce Cox-2 expression. Neither in undifferentiated nor in differentiated NG108 cells was Cox-2 induced by any of these treatments (Fig. 1d). Protein obtained from rat mesangial cells stimulated with lysophosphatidic acid (Reiser et al. 1998) was used as a positive control. The same negative results were also obtained in N2a cells.

Increased induction of Cox-1 mRNA and protein by dexamethasone

Incubation of NG108 cells with dexamethasone (10^{-6} M) only marginally affected Cox-1 mRNA expression (Fig. 2a). However, dexamethasone significantly enhanced Cox-1 mRNA expression when the cells were stimulated with a combination of retinoic acid and dexamethasone (Dex, 10^{-6} M) for 24 and 48 h. Cox-1 protein was detected in the cellular homogenates by western blot analysis. Two parallel incubations of a representative experiment are shown. (c) NG108 cells were incubated with retinoic acid (RA, 20 μM) and dexamethasone (Dex, 10^{-6} to 10^{-7} M) as indicated for 48 h. Cox activity was determined by incubation of the cells with arachidonic acid for 30 min and subsequent determination of PGE2 in the cell culture supernatants. Data are means of triplicate incubations determined in duplicate. *p < 0.05 compared with cells treated with retinoic acid, two-sided Student’s t-test for independent samples.
24 or 48 h, and neither increased or decreased significantly (data not shown). Induction of Cox-1 mRNA by dexamethasone was concentration dependent and reached a maximum at 1–2 \( \text{mM} \) (Fig. 2c).

At the protein level, the increase in Cox-1 expression was delayed compared with the mRNA induction. Protein expression after 24 h was variable (Fig. 3a, N2a cells after 24 and 48 h). Increased levels of Cox-1 protein were consistently observed in both cell lines after 48 h of incubation with dexamethasone plus retinoic acid (Fig. 3a, N2a cells; Fig. 3b, NG108 cells). Compared with cells treated with retinoic acid only, dexamethasone elevated Cox-1 protein levels about threefold (2.9 ± 1.0-fold increase in NG108 cells compared with retinoic acid; means ± SD, \( n = 3 \) experiments). A similar increase was also observed after 72 h (data not shown).

In order to assess Cox activity, the cells were incubated for a short period of time (30 min) with exogenous arachidonic acid. Prostaglandin \( \text{E}_2 \) immunoreactivity was determined in the cell culture supernatants. Increased cyclooxygenase activity was observed when the cells were incubated with retinoic acid plus dexamethasone for 48 h (Fig. 3c).

Morphologically, cells treated with retinoic acid plus dexamethasone were indistinguishable from cells treated with retinoic acid only.

**Regulation of Cox-1 induction by dexamethasone**

Cyclooxygenase-1 expression was also enhanced by dexamethasone when the cells were differentiated with retinoic acid for 48 h before adding dexamethasone for the following 24 h (Fig. 4a). Expression of Cox-1 mRNA of cells treated with retinoic acid alone was not changed during this time. These experimental conditions therefore allowed us to separate the induction of Cox-1 by dexamethasone from the induction by retinoic acid. An increase in Cox-1 expression was reproducibly detected within 6 h of incubation with dexamethasone. Under these conditions, cycloheximide was used to inhibit protein synthesis. *De novo* protein
synthesis proved to be necessary for the induction of Cox-1 mRNA expression by dexamethasone (Fig. 4b).

Enhanced levels of mRNA may be caused by increased transcriptional activity and/or increased messenger stability. To assess transcriptional activity, NG108 cells were transiently transfected with a luciferase-coupled promoter construct containing about 2 kb of the mouse Cox-1 promoter. After transfection, a basal level of luciferase activity was measurable in NG108 cells (Fig. 5a, Co). Basal luciferase expression was barely affected when the cells were incubated for 24 h with medium or medium + DMSO (Fig. 5a). Stimulation with retinoic acid consistently increased luciferase activity. Cells incubated with dexamethasone alone, or in combination with retinoic acid, showed a slightly elevated luciferase activity, which did not reach statistical significance.

The small effect of dexamethasone on transcriptional activity determined by promoter analyses suggested an effect of the glucocorticoid on Cox-1 mRNA stability. To study this hypothesis, NG108 cells were pretreated with retinoic acid in the presence or absence of dexamethasone for 24 h and then were incubated with an inhibitor of transcription, DRB, for 12–24 h. The half-life of Cox-1 mRNA in retinoic acid-stimulated cells was 12 h (Fig. 5b). Dexamethasone increased the stability of Cox-1 mRNA extending the half-life to about 20 h.

### Specificity of Cox-1 up-regulation by corticosteroids

NG108 cells were treated with different types of steroids like hydrocortisone, aldosterone, progesterone and oestrogen. Hydrocortisone, which has a lower receptor affinity than dexamethasone, increased the retinoic acid-mediated induction of Cox-1 to a lesser extent than dexamethasone (Figs 6a and b). Aldosterone proved to be as potent as dexamethasone. Within 24 h, incubation of NG108 cells with retinoic plus aldosterone (10^{-6} or 10^{-7} M) induced Cox-1 mRNA expression 2.2 ± 0.5-fold when compared with retinoic acid (means ± SD, n = 4 experiments, p < 0.05, two-sided paired Student’s t-test). No significant difference was observed between 10^{-6} and 10^{-7} M aldosterone. In contrast to these corticosteroids, equimolar concentrations of progesterone did not significantly induce Cox-1 (data not shown). A minor induction of Cox-1 mRNA was observed in some experiments but did not reach statistical significance. Oestrogen at concentrations up to 10^{-6} M was ineffective, as were the aminosteroids dihydroepiandrostosterone and dihydroepiandrostosterone sulfate (Fig. 6 and data not shown). Effects of corticosteroids are primarily mediated by intracellular steroid receptors, but membrane receptors have also been reported (Towle and Sze 1983; Orchinik et al. 1997). The glucocorticoid receptor antagonist RU486 itself had no effect on Cox-1 mRNA expression, but antagonized the induction of Cox-1 by dexamethasone, aldosterone and hydrocortisone (Figs 6a and b).

### Discussion

Modulation of cyclooxygenases by corticosteroids has been described in many cellular systems. In most instances, down-regulation of the inducible Cox-2 was observed with little effect on Cox-1. In the present study we show up-regulation of Cox-1 during the retinoic acid-mediated differentiation of two neuroblastoma cell lines, NG108 and N2a, which was increased by corticosteroids.

Differentiation of the neuroblastoma cell lines NG108 and N2a by retinoic acid induced a moderate up-regulation of Cox-1 mRNA during the first 24 h of incubation. A similar differentiation-associated induction of Cox-1 has been previously described in PC12 cells, treated with nerve growth factor (Kaplan et al. 1997). Up-regulation of Cox-1 is not restricted to neuronal differentiation, but was also described in phorbol ester-treated monocytes (Hoff et al. 1993) or activin A- and retinoic-acid-treated macrophages (Nusing et al. 1995). Changes of Cox-1 expression during ontogeny are commonly observed, e.g. during T-cell development (Rocca et al. 1999), lung maturation (Brannon et al. 1994) or renal glomerulogenesis (Komhoff et al. 1995).
The functional implications of these changes, however, remain rather speculative, as Cox-1 knockout mice have no signs of developmental abnormalities, possibly as a result of compensatory Cox-2 activity (Langenbach et al. 1995; Kirtikara et al. 1998).

In undifferentiated or differentiated neuroblastoma cell lines, no Cox-2 expression was detected. Even treatment with stimuli such as dibutyryl cAMP, calcium ionophore A23187 or phorbol ester, which are potent inducers of Cox-2 in other cell types, had no effect in these cells. These results are in contrast with data obtained in NG108 cells transiently transfected with a Cox-2 promoter construct containing 963 bp of the mouse Cox-2 promoter coupled to luciferase, which was activated by retinoic acid (Bazan et al. 1994). In other cellular systems, repression rather than induction of Cox-2 expression by retinoic acid was observed (Mestre et al. 1997). A similar failure to detect Cox-2 was reported in PC12 cells and was suggested to be caused by a mutation preventing successful transcription (Arenander et al. 1989; McGinty et al. 2000). This might also be an explanation for the results obtained with the neuroblastoma cell lines used in this study, but has yet to be proven.

Up-regulation of Cox-1 by glucocorticoids was observed at the mRNA and protein level and caused increased Cox activity. Pre-incubation of the cells with cycloheximide prevented dexamethasone-mediated Cox-1 induction, indicating that Cox-1 was not a primary target of the corticosteroid receptor. The indirect effect of corticosteroids on Cox-1 expression may be the basis of the cell-specific interference with Cox-1 expression: glucocorticoids inhibited the up-regulation of Cox-1 in monocyctic cell lines (Hoff et al. 1993) and fetal pulmonary artery endothelial cells (Jun et al. 1999). Dexamethasone-mediated up-regulation of Cox-1 was observed in bone-marrow-derived mast cells, when the steroid was combined with stem-cell factor, but not with interleukin-3 (Samet et al. 1995). In osteoclast-supporting stromal cells, Cox-1 was up-regulated when 1,25-dihydroxy vitamin D3 and dexamethasone were combined (Adams et al. 1999). Up-regulation of Cox-1 thus seems to depend on at least two signals, one corticosteroid dependent and a second possibly cell-specific signal. It remains speculative, whether the same protein or set of proteins is induced by dexamethasone in these different cell types.

The increase in Cox-1 mRNA was a result of complex regulation. Retinoic acid increased transcriptional activity, whereas only a small effect was observed when the cells were treated with dexamethasone. Compared with retinoic acid alone, dexamethasone enhanced the stability of Cox-1 mRNA. The half-life determined in the presence of DRB was increased from 12 to 20 h. Up-regulation of Cox-1 mRNA, mediated by the indirect glucocorticoid action, thus seems to depend on multiple molecular mechanisms, including increased transcriptional activity and enhanced mRNA stability.

Cyclooxygenase-1 expression was induced by the synthetic glucocorticoid dexamethasone, but also by the endogenous corticosteroids hydrocortisone and aldosterone. In vivo, aldosterone is a specific agonist of the mineralocorticoid receptor, whereas hydrocortisone, and to a lesser extent dexamethasone, bind to mineralocorticoid and glucocorticoid receptors, although with different affinities (De Kloet et al. 1999). Both receptors are present in neuronal cells, with prominent expression in the hippocampus (Kawata 1995). RU486 is a specific inhibitor of progesterone and glucocorticoid receptors, but has no affinity for the aldosterone receptor (Agarwal et al. 1987; Agarwal 1994). In the present study, RU486 was used to distinguish between genomic and non-genomic effects of the corticosteroids. Up-regulation of Cox-1 mRNA expression by hydrocortisone and dexamethasone was completely inhibited by RU486, indicating the involvement of the glucocorticoid receptor and excluding effects mediated by membrane receptors, which have been described in neuronal membranes (Towle and Sze 1983; Orchinik et al. 1997). The reduction of aldosterone-mediated up-regulation of Cox-1 by RU486 was rather unexpected, suggesting the interaction of aldosterone and RU486 with the same receptor, not excluding indirect functional interference. There are several publications reporting an interference of RU486 with aldosterone effects in other cell types (e.g. Sakly et al. 1984; Chang and Perlman 1987; Zach et al. 1993; Ebata et al. 1999). It was suggested that under certain conditions, aldosterone might interact with the glucocorticoid receptor, although with low affinity (Schmidt et al. 1993). None of the other studies dealing with Cox-1 regulation by glucocorticoids investigated aldosterone. The corticosteroid receptors present in the neuroblastoma cell lines have not been characterized. Therefore, the corticosteroid-induced up-regulation of Cox-1 cannot be interpreted in more detail.

Oestrogens or the neurosteroids dihydroepiandrosterone and dihydroxyandrostenedione sulfate did not affect Cox-1 expression, whereas a small effect of progesterone was detected in some experiments. The progesterone receptor binds to the same response elements as do the aldosterone and glucocorticoid receptor, which may explain a partial glucocorticoid agonistic action of progesterone (summarized in Turner 1997). The data presented in this study are based on in vitro experiments. At the present stage it is premature to speculate about the in vivo equivalent. Cyclooxygenase-1 is located in distinct areas of the brain and has been shown to be regulated during brain development (Kawasaki et al. 1993; Peri et al. 1995). Modulation by brain corticosteroids may well play a role during these processes, given the functional role of prostanoids in the regulation of wakefulness or stress response. Over-expression of Cox-2 in PC12 cells protected
these cells from serum-withdrawal apoptosis (McGinty et al. 2000). Furthermore, it has recently been shown that Cox-2 inhibited cell-cycle progression in a variety of cell types by a mechanism that was independent of prostanooid synthesis (Trifan et al. 1999). It is not clear whether these findings are restricted to Cox-2 or might also be relevant for the interpretation of the physiological role of Cox-1. As in most tissues, corticosteroids interfere with the induction of the inducible Cox-2 expression in brain neurones (Yamagata et al. 1993). Our data suggest that corticosteroids differentially regulate Cox-1 and Cox-2, which are both present in the brain under physiological conditions.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft, SFB 353, A2.

References


