Evaluation of coexpression of microsomal prostaglandin E synthase-1 and cyclooxygenase-2 in interleukin-1–stimulated equine articular chondrocytes

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Objective—To characterize expression of cyclooxygenase-2 (COX-2) and microsomal prostaglandin E synthase-1 (mPGES-1) and regulation of prostaglandin E2 (PGE2) production by equine articular chondrocytes.

Sample Population—Articular cartilage from the metacarpophalangeal joints of 7 adult horses.

Procedure—Equine chondrocyte monolayer cultures were stimulated with different concentrations (2.5, 5, 10, and 20 ng/mL) of recombinant human interleukin-1β (rhIL-1β) for 24 hours and then with rhIL-1β (5 ng/mL) for 3, 6, 9, 12, and 24 hours. Concentration of PGE2 in the media was measured via radioimmunoassay. Total RNA was extracted from harvested chondrocytes, and regulation of COX-2 and mPGES-1 mRNA was studied via reverse transcriptase-polymerase chain reaction assay and Southern blot analysis with equine-specific probes. Western blot analyses were performed on cellular extracts to characterize expression of COX-2 and mPGES-1 protein.

Results—Stimulation with 5, 10, and 20 ng/mL of rhIL-1β caused a significant increase in PGE2 concentrations in the culture media, and incubation of cells with rhIL-1β (5 ng/mL) for 6 to 24 hours increased PGE2 production significantly. The increase in prostaglandin production was associated with an induction of COX-2 and mPGES-1 transcripts. There was also a rhIL-1β–dependent induction in COX-2 and mPGES-1 protein expression.

Conclusions and Clinical Relevance—Collectively, results indicated that the rhIL-1β–dependent increase in PGE2 production in equine chondrocytes in monolayer culture was associated with coordinated upregulation of COX-2 and mPGES-1 expression. The pathophysiologic consequences of upregulated COX-2 and mPGES-1 expression and of PGE2 synthesis in rhIL-1β–stimulated equine chondrocytes remain to be elucidated. (Am J Vet Res 2005;66:1985–1991)

Studies on the pathophysiology of osteoarthritis provide evidence that inflammatory mediators have an important role in the initiation and progression of the disease. Mediators exert their effects in the cartilage matrix but also on other joint tissues. Proinflammatory cytokines induce the development and enhance the progression of lesions of osteoarthritis. The proinflammatory cytokine interleukin-1β (IL-1β) is produced by joint cells during osteoarthritis and is present in large amounts in synovial fluid of horses with osteoarthritis. Affected human cartilage releases sufficient amounts of IL-1β to promote cartilage degradation while inhibiting its repair, leading the affected cartilage to an autodestructive pathway. Results of many studies indicate that IL-1 not only induces the synthesis of degradative proteinases by synovial cells and chondrocytes but also induces prostaglandin E2 (PGE2), a major mediator of inflammation.

Increased concentrations of PGE2 during naturally occurring disease or after cytokine stimulation have a central role in the development and progression of osteoarthritis. It has been recently reported that PGE2 induces apoptosis of bovine articular chondrocytes and that its production is required for caspase-dependent chondrocyte death induced by nitric oxide in affected canine and human chondrocytes. Additionally, PGE2 stimulates production of matrix metalloproteinases (MMPs) and could be responsible, in part, for the degradation of proteoglycans in affected joints. Furthermore, PGE2 can cause bone resorption and also may be involved in osteophyte formation encountered in osteoarthritis patients. Taken together, these studies suggest a role for PGE2 in the progression of osteoarthritis.

Prostaglandin E2 is produced by the activity of 2 important enzymes, cyclooxygenase (COX) and PGE synthase (PGES), in the arachidonic acid pathway. Prostaglandin E synthase converts the product of the COX enzymes, PGH2, into PGE2. Two major isomers of COX and PGES exist. The constitutive pathway is formed by COX-1 and the cytosolic isofrom of PGES. The inducible pathway, responsible for increased produc-
tion of PGE2, in inflammatory processes, includes COX-2 and the recently identified microsomal isoform of PGES (mpGES). Different forms of mpGES have also been isolated: mpGES-1 and mpGES-2. Microsomal PGES-1, recently characterized and cloned, is selectively upregulated during COX-2–dependent PGE2 production in the rat adjuvant-induced arthritis model. Microsomal PGES-1 is also upregulated with COX-2 after IL-1β or tumor necrosis factor (TNF)-α stimulation in human chondrocytes affected by osteoarthritis, regardless of whether mpGES-2 remains constitutively expressed and unaffected by proinflammatory stimulation. Moreover, mpGES-1 inhibition at the gene level can decrease the severity of cartilage lesions seen in mpGES-1–deficient mice after experimentally induced inflammatory arthritis. The results of these studies suggest an important role for mpGES-1 induction in joint disease.

Our hypothesis, based on the knowledge that COX-2 is upregulated in equine articular chondrocytes by a proinflammatory stimulus, was that proinflammation would increase COX-2 and mpGES-1 mRNA and protein expression. The objective of our study was to characterize the expression of COX-2 and mpGES-1 and the regulation of PGE2 production by normal equine articular chondrocytes.

Materials and Methods

Source of tissues and cell culture—Macroscopically normal articular cartilage was aseptically harvested from the weight-bearing surface of the metacarpophalangeal joints of 7 adult (10 to 15 years old) Standardbreds, obtained at an abattoir. Chondrocytes were isolated via 2 sequential digestions with trypsin and collagenase. Briefly, full-thickness cartilage slices were washed 3 times with Dulbecco modified Eagle medium that contained penicillin (400,000 U/L), streptomycin (400 µg/L), gentamicin (150 µg/L), and HEPES buffer (0.02M). Cartilage slices were incubated at 37°C and gently agitated with sterile tryptic solution (0.05% trypsin and 0.01% EDTA) for 25 minutes and subsequently with collagenase solution (0.05% collagenase and 10% fetal bovine serum) for 11 to 13 hours. The supernatant was filtered with a 70-µm cell strainer, and the cells were washed with HEPES buffer (0.02M). Cartilage slices were incubated at 37°C, homogenized, and stored at –70°C until further analysis. The fresh cell strainer was removed. The RNA was precipitated with 100% ethanol, centrifuged, and washed with 70% ethanol. After ethanol evaporation, the RNA was resuspended in sterile diethyl pyrocarbonate water and quantified spectrophotometrically.

Three sizes of culture dishes were used to accommodate the need of sufficient materials for different analyses. Twenty-four–well culture plates were used for studies designed to measure changes in PGE2 production in the culture media. Six-well plates were used for analyses requiring RNA extracts, whereas large culture dishes (10 cm in diameter) were used in selected experiments to provide sufficient protein extracts for western blots. Cells were seeded as 1, 3, and 5 mL of chondrocyte solution (0.5 × 10^6 cells/mL) to a 24-well plate, 6-well plate, and 10-cm culture dish, respectively. All culture plates were incubated in a humid, 3% CO2, 37°C incubator until cells adhered to the wells. The culture media was changed every 48 hours until chondrocytes reached confluence. Twenty-four hours prior to the recombinant human IL-1β stimulation, cells were cultured in serum-free media.

Study design—In experiment 1, 4 horses were used. Equine chondrocytes cultured in 24-well plates were stimulated with 0 (control), 2.5, 5, 10, and 20 ng/mL of rhIL-1β for 24 hours to study the effect of the cytokine on PGE2 production. Each treatment was performed in duplicate wells, and the study was replicated twice with 2 horses. A similar dose–response study was performed to characterize the regulation of COX-2 and mpGES-1 mRNA by use of chondrocytes cultured in 6-well plates for 24 hours in the presence of 0 (control), 2.5, 5, 10, and 20 ng/mL of rhIL-1β. The latter study was repeated twice on 2 other horses.

In experiment 2, a group of 3 horses was used. The time-dependent regulation of PGE2 production and of COX-2 and mpGES-1 mRNA expression by rhIL-1β (5 ng/mL) was characterized in equine chondrocytes cultured for 0, 3, 6, 9, 12, and 24 hours. For the PGE2 production, cells were cultured in 24-well plates and each time point analysis was performed in duplicate wells, whereas the regulation of COX-2 and mpGES-1 mRNA was studied in cells cultured in 6-well plates. The regulation of COX-2 and mpGES-1 protein by rhIL-1β (5 ng/mL) was performed by use of 10-cm culture dishes but only on selected time points (0, 12, and 24 hours of culture) because of limited numbers of cells. These analyses were replicated 3 times with 3 other horses.

PGE2 measurement—At the end of the culture period, the media were frozen at –70°C until further analysis. Samples were collected at each concentration or time point and analyzed separately. Concentrations of PGE2 were measured directly in culture media by use of a specific radiomunoassay, as described. The antisera used had cross-reactivities against PGE1, PGF2α, PGF2β, and 6-keto PGF1α of 70%, 1.4%, 0.7%, and 0.6%, respectively. The sensitivity of the assay was 40 pg/mL, and the intra- and interassay coefficients of variation were 6.3% and 8.6%, respectively.

Semi-quantitative reverse transcriptase-polymerase chain reaction and Southern blot analysis—At the end of the culture period, cells were harvested in 1 mL of Trizol reagent, homogenized, and stored at –70°C until further analysis. The Trizol reagent that contained the cell lysate was incubated at 20°C for 5 minutes. Chlorof orm was added to the solution, which was vigorously agitated, and a second incubation was performed for 3 minutes. Following centrifugation, the aqueous phase that contained the RNA was removed. The RNA was precipitated with 100% ethanol and washed with 70% ethan ol. After ethanol evaporation, the RNA was resuspended in sterile diethyl pyrocarbonate water and quantified spectrophotometrically.

A commercial reverse transcriptase-polymerase chain reaction system was used for semiquantitative analysis of COX-2 and mpGES-1 mRNA. Reactions were performed as directed by the manufacturer with sense (5'-GAG CAG GCT CAT ACT GAT AGG AG-3') and antisense (5'-GAG TGC TTC TAA CTC CGC AGC G-3') primers specific for equine COX-2, sense (5'-AAC GAC ATG GAG ACC ATC TAC C-3') and antisense (5'-TCT TGA CTC CTC TTC TCT A-3') primers specific for equine mpGES-1, and sense (5'-ATC ACC ATC TTC CAG GAG CGA GA-3') and antisense (5'-GTC TTC TGG GTG GCA ATG G-3') primers specific for equine glyceraldehyde-3-phosphate dehydrogenase (GAPDH). These reactions resulted in the production of COX-2, mpGES-1, and GAPDH cDNA fragments of 489, 476, and 341 bp, respectively. Each reaction was performed with
100 ng of total RNA, and cycling conditions were 1 cycle of 48°C for 45 minutes and 94°C for 2 minutes, followed by a variable number of cycles of 94°C for 30 seconds, 58°C for 1 minute, and 68°C for 2 minutes. The number of cycles used was optimized for each gene to fall within the linear range of polymerase chain reaction amplification and was 16 cycles for COX-2 and GAPDH and 18 cycles for mPGES-1. After polymerase chain reaction amplification, samples were electrophoresed on 2% tris-acetic acid-EDTA-agarse gels, transferred to nylon membranes, and hybridized with corresponding radiolabeled COX-2, mPGES-1, and GAPDH cDNA fragments with a hybridization solution, as described. Membranes were exposed to a phosphor screen, and signals were quantified on an imaging system by use of software.

Western blot analyses—Solubilized cell extracts and western blot analyses were performed as described. Briefly, cells were homogenized and sonicated on ice in TED (20mM Tris [pH, 8.0], 50mM EDTA, and 0.1mM diethylthiocarbamic acid) buffer that contained 1.0% Tween (polyoxyethylene-sorbitan-monolaurate). The sonicates were centrifuged at 16,000 X g for 15 minutes at 4°C. The recovered supernatant (whole-cell extract) was stored at -70°C until electrophoretic analyses were performed. Protein concentration was determined by the method of Bradford. Samples (100 µg of proteins) were resolved by 1-dimensional SDS-PAGE and electrophoretically transferred to polyvinylidene difluoride membranes. Blocking of membranes was done with 5% nonfat dry milk in 0.1% TTBS (0.1% Tween-20 and 10mM Tris-buffered saline [pH, 7.5]) for 1 hour at 20°C, then washed twice for 2 minutes at 20°C with 0.1% TTBS. After blockage, membranes were incubated with a selective anti–COX-2 antibody (MF243 at 1:7,500 dilution) or anti–mPGES-1 antibody (1:1,000 dilution) for use of software.

Statistical analyses—A 2-way ANOVA, with horse identity and concentration of rhIL-1β included as factors, was used to test for effects of rhIL-1β on PGE2 production. When the ANOVA indicated a significant (P < 0.05) difference, Tukey post hoc tests were used to compare pairs of means. An ANOVA with concentrations of PGE2 at time 0 as a cofactor and time, horse identity, and treatment as factors was performed for time-dependent analysis of PGE2 production. When PGE2 concentration was analyzed with concentrations of PGE2 at time 0 as a cofactor and time, horse identity, and treatment as factors was performed for time-dependent analysis of PGE2 production. A value of P < 0.05 was considered to be significant. The data were analyzed with software.

Results

IL-1β-dependent induction of PGE2 production in experiment 1—Equine articular chondrocytes produced low amounts of PGE2 under nonstimulated culture conditions (control) or after stimulation with 2.5 ng/mL of rhIL-1β for 24 hours. There was a significant effect of rhIL-1β concentration on PGE2 production (P < 0.001). Post hoc tests revealed that PGE2 production was significantly lower in the chondrocyte group under nonstimulated culture conditions and in the group stimulated with 2.5 ng/mL of rhIL-1β than in the 5, 10, and 20 ng/mL stimulated groups (P = 0.01).

IL-1β-dependent induction of COX-2 and mPGES-1 mRNA expression in experiment 1—Amounts of COX-2 and mPGES-1 mRNA were low or undetectable in nonstimulated culture conditions (control; 0 ng/mL; Figure 1). Cyclooxygenase-2 mRNA expression was induced by rhIL-1β. Likewise, mPGES-1 mRNA expression was also induced after rhIL-1β stimulation.
proteins in experiment 2
mRNA expression between 3 and 24 hours of culture.
stimulations, but stimulation with rhIL-1
amounts of mPGES-1 transcript under control condi-
sion was maintained throughout the 24-hour culture
pared with controls, and this pattern of COX-2 expres-
ion was revealed by use of western blot analysis
stimulation. Similarly, induction of mPGES-1 protein
protection from earlier studies315 of normal human chondrocytes and, more recently, equine chondrocytes.15,39 A significant increase in PGE₂ concentrations was not observed until 6 hours after rhIL-1β treatment. The apparent delay observed between the rapid induction of COX-2 mRNA (3 hours after rhIL-1β) and the detection of a significant increase in PGE₂ production (6 hours after rhIL-1β) was likely related to the time required for translation of COX-2 mRNA into COX-2 protein and for accumulation of PGE₂ in the culture media. This induction of COX-2 transcript was also associated with increased COX-2 protein, as observed by others.39 In contrast, a more gradual increase in COX-2 induction was observed in IL-1β-stimulated human chondrocytes, with maximal concentrations observed only at 24 hours after stimulation.37 This slower response in gene expression may be related to the normal versus diseased status of the cells, differences in IL-1β concentrations used among studies, species differences, or the use of human IL-1β on equine cells. Collectively, these results may be relevant to the pathophysiologic features of osteoarthritis because IL-1β-dependent COX-2 induction of PGE₂ synthesis is thought to modulate cartilage destruction.38 Furthermore, COX-2 can be induced by IL-1β in many tissues affected by osteoarthritis, including synovial fibroblasts, chondrocytes, meniscal chondrocyte-like cells, and osteophytic chondrocytes,35 delineating the importance of this inducible enzyme in the production of pathologic concentrations of PGE₂ in joint disease.

The metabolism of arachidonic acid by COX-1 and -2 yields the intermediary product PGH₂, which is rapidly converted into PGE₂, PGD₂, PGF₂α, PGF₁α, and thromboxane A₂ by specific terminal synthases. Chondrocyte PGE₂ synthesis is markedly induced by IL-1β or TNF-α39; however, to our knowledge, expression of PGES has not been previously studied in equine articular tissues. In other species, the inducible form of the enzyme, mPGES-1, is upregulated by lipopolysaccharide, IL-1β, and TNF-α.29 Microsomal PGES-1 may therefore be an important enzyme in inflammatory events. The rapid expression of mPGES-1 mRNA after IL-1β stimulation in the present study suggests a role for the enzyme in early PGE₂-dependent inflammatory events in equine joint disease. In a rat adjuvant-induced arthritis model, mPGES-1 is selectively upregulated during COX-2-dependent PGE₂ production.30 Following these recent findings, mPGES-1 was considered the isoform functionally linked to COX-2 and responsible for the pathologic production of PGE₂ in vivo.31 Additional lines of evidence for a major role of mPGES-1 in arthritis are provided by results of genetic studies in which mPGES-1–deficient mice evaluated in a collagen-induced arthritis model had a reduced inflammatory response and protection from cartilage

Results of experiment 1 indicated that rhIL-1β used at 5 ng/mL led to significant (P = 0.01) production of PGE₂ in the media and induced COX-2 and mPGES-1 mRNA expression. Therefore, except for controls, subsequent chondrocyte cultures in experiment 2 were performed with 5 ng/mL of rhIL-1β.

Time-dependent regulation of PGE₂ production in experiment 2—Control cells produced low or negligible amounts of PGE₂ between 0 and 24 hours of culture (Figure 2). In contrast, rhIL-1β stimulated PGE₂ production by equine chondrocytes cultured for 6 to 24 hours. A significant (P < 0.001) effect of treatment and time on PGE₂ production was detected. Post hoc tests revealed a significant (P < 0.001) difference between treatment and control samples at all time points, except 3 hours after stimulation. The cumulative PGE₂ production increased progressively until 24 hours to attain a mean value of 368 ng/mL.

Time-dependent expression of COX-2 and mPGES-1 mRNA in experiment 2—The chondrocytes did not express COX-2 mRNA under control culture conditions (Figure 3). In contrast, a rapid induction of COX-2 mRNA was observed 3 hours after rhIL-1β, compared with controls, and this pattern of COX-2 expression was maintained throughout the 24-hour culture period. Similarly, chondrocytes expressed negligible amounts of mPGES-1 transcript under control conditions, but stimulation with rhIL-1β induced mPGES-1 mRNA expression between 3 and 24 hours of culture.

Time-dependent expression of COX-2 and mPGES-1 proteins in experiment 2—Equine articular chondrocytes expressed low or negligible amounts of COX-2 or mPGES-1 proteins under control culture conditions (Figure 4). In contrast, a strong expression of COX-2 protein was observed after 12 and 24 hours of rhIL-1β stimulation. Similarly, induction of mPGES-1 protein expression was revealed by use of western blot analysis after 12 and 24 hours following the rhIL-1β stimulation.

Discussion
Results of this study provided evidence that the recently identified microsomal prostaglandin synthase, mPGES-1, a terminal enzyme in the arachidonic acid pathway that metabolizes PGH₁ to PGE₂, was inducible by the proinflammatory cytokine IL-1β and functionally linked with COX-2 in equine articular chondrocytes in monolayer culture. These results agreed with those recently published37 for human chondrocytes affected by osteoarthritis and suggest that mPGES-1 could be a downstream therapeutic target for developing more selective blockade of PGE₂ synthesis, thereby possibly avoiding adverse effects reported for COX-1 and -2 inhibitors.

The maximal induction of COX-2 mRNA observed at 3 hours after rhIL-1β stimulation and its sustained expression for at least 24 hours agreed with findings from earlier studies315 of normal human chondrocytes and, more recently, equine chondrocytes.15 A significant increase in PGE₂ concentrations was not observed until 6 hours after rhIL-1β treatment. The apparent delay observed between the rapid induction of COX-2 mRNA (3 hours after rhIL-1β) and the detection of a significant increase in PGE₂ production (6 hours after rhIL-1β) was likely related to the time required for translation of COX-2 mRNA into COX-2 protein and for accumulation of PGE₂ in the culture media. This induction of COX-2 transcript was also associated with increased COX-2 protein, as observed by others.39 In contrast, a more gradual increase in COX-2 induction was observed in IL-1β-stimulated human chondrocytes, with maximal concentrations observed only at 24 hours after stimulation.37 This slower response in gene expression may be related to the normal versus diseased status of the cells, differences in IL-1β concentrations used among studies, species differences, or the use of human IL-1β on equine cells. Collectively, these results may be relevant to the pathophysiologic features of osteoarthritis because IL-1β-dependent COX-2 induction of PGE₂ synthesis is thought to modulate cartilage destruction.38 Furthermore, COX-2 can be induced by IL-1β in many tissues affected by osteoarthritis, including synovial fibroblasts, chondrocytes, meniscal chondrocyte-like cells, and osteophytic chondrocytes,35 delineating the importance of this inducible enzyme in the production of pathologic concentrations of PGE₂ in joint disease.

The metabolism of arachidonic acid by COX-1 and -2 yields the intermediary product PGH₂, which is rapidly converted into PGE₂, PGD₂, PGF₂α, PGF₁α, and thromboxane A₂ by specific terminal synthases. Chondrocyte PGE₂ synthesis is markedly induced by IL-1β or TNF-α39; however, to our knowledge, expression of PGES has not been previously studied in equine articular tissues. In other species, the inducible form of the enzyme, mPGES-1, is upregulated by lipopolysaccharide, IL-1β, and TNF-α.29 Microsomal PGES-1 may therefore be an important enzyme in inflammatory events. The rapid expression of mPGES-1 mRNA after IL-1β stimulation in the present study suggests a role for the enzyme in early PGE₂-dependent inflammatory events in equine joint disease. In a rat adjuvant-induced arthritis model, mPGES-1 is selectively upregulated during COX-2-dependent PGE₂ production.30 Following these recent findings, mPGES-1 was considered the isoform functionally linked to COX-2 and responsible for the pathologic production of PGE₂ in vivo.31 Additional lines of evidence for a major role of mPGES-1 in arthritis are provided by results of genetic studies in which mPGES-1–deficient mice evaluated in a collagen-induced arthritis model had a reduced inflammatory response and protection from cartilage
and bone changes normally associated with this model. An interesting possibility for therapeutic intervention is the eventual specific blockade of mPGES-1 expression by articular cells to treat inflammatory and degenerative joint diseases.

The profile of PGE2 synthesis observed in the present study was in agreement with the previously reported temporal increase in PGE2 production after IL-1β stimulation of normal chondrocytes. Increased PGE2 has been measured in equine joints with degenerative arthropathies and reported to be a good to excellent predictor of pathologic findings in equine joints. The potential role played by PGE2 in the pathophysiology of osteoarthritis is emerging. Prostaglandin E2 induces chondrocyte apoptosis, enhances glutathione peroxidase activity, and decreases the degradation of proteoglycans in vitro. E2 induces chondrocyte apoptosis, enhances production of MMPs, and decreases the synthesis and promotes degradation of proteoglycans in vitro. Furthermore, it causes osteoclastic bone resorption and could alter subchondral bone in osteoarthritis. Interestingly, PGE2 also enhances its own IL-1β-induced production by rheumatoid synovial fibroblasts, highlighting a potential positive feedback loop.

Paradoxically, beneficial effects of PGE2 on joint structures have also been identified. The addition of exogenous PGE2 to equine or human chondrocytes decreases the IL-1β–induced expression of MMP-1, MMP-3, MMP-13, and tissue inhibitor of MMP-1, indicating that PGE2 could be beneficial in inflammatory joint diseases. However, the concentrations of exogenous PGE2 that provided an effect were in the picogram per milliliter range. Considering that the concentrations of PGE2 detected in synovial fluids of equine arthropathies are in the picogram per milliliter range, the clinical relevance of these putative beneficial effects will require further investigation. Other arachidonic acid metabolites appear to be important for the homeostasis of cartilage, as in other organs. The prostaglandin 15-deoxy-delta 12,14 PGJ2, a metabolite of the prostaglandin PGD2, inhibits IL-1β–induced nitric oxide synthase expression and MMP-13 production in chondrocytes affected by osteoarthritis. Similarly, PGJ2 inhibits IL-1β–induced PGE2 production and COX-2 expression by affected human chondrocytes. Presently, nonsteroidal anti-inflammatory drugs, commonly used to control inflammation in joint disease, block upstream enzymes in the arachidonic acid pathway and may concurrently block all potentially beneficial prostaglandins. The realization that COX-2 was a key enzyme in prostaglandin synthesis led to the development of COX-2–selective inhibitors. Because serious adverse effects are recognized with their use, more selective inhibitors of PGE2 synthesis may be clinically useful because they would spare the production of arachidonic acid metabolites, which are important for the homeostasis of joints and many organs. Microsomal PGES-1 could be a potential candidate to achieve this goal.

The effect of the cytokine on all constituents of the equine joint, as well as the pathophysiologic consequence of COX-2 and mPGES-1 induction in equine chondrocytes, deserves further investigation. Selective blockade of mPGES-1 expression might provide an interesting therapeutic strategy for the control of PGE2 production in equine joint diseases.

References


