Expression and Vascular Effects of Cyclooxygenase-2 in Brain

Johnny E. Brian, Jr, MD; Steven A. Moore, MD, PhD; Frank M. Faraci, PhD

Background and Purpose—Cyclooxygenase-2 (COX-2) is an inducible isoform of cyclooxygenase. Several types of brain cells in culture can express COX-2 when treated with lipopolysaccharide (LPS) or some cytokines. LPS produces dilatation of cerebral arterioles in vivo through a mechanism that is partially inhibited by indomethacin. In the present study we examined the hypothesis that LPS causes increased expression of COX-2 in brain as well as COX-2–dependent dilatation of cerebral arterioles.

Methods—Cranial windows were implanted in anesthetized rats and used to measure diameter of cerebral arterioles under control conditions and during topical application of various agonists and antagonists. Windows were flushed every 30 minutes for 4 hours with vehicle (artificial cerebrospinal fluid; n=5), LPS (100 ng/mL; n=8), LPS and NS-398 (100 μmol/L; n=8), a selective inhibitor of COX-2, or LPS and dexamethasone (1 μmol/L; n=5), which attenuates expression of COX-2. To examine expression of COX-2 protein in vivo, other animals were injected intracisternally with artificial cerebrospinal fluid (n=3) or LPS (40 ng; n=4). Four hours after injection, the leptomeninges were harvested and analyzed by Western blot for expression of COX-2 protein. In a third group of experiments, COX-2 expression and prostaglandin E2 (PGE2) production were determined in leptomeningeal tissue treated for 4 hours ex vivo with vehicle (n=4), LPS (100 ng/mL; n=4), LPS and NS-398 (100 μmol/L; n=4), or LPS and dexamethasone (1 μmol/L; n=4).

Results—LPS caused marked, progressive dilatation of cerebral arterioles, with a maximum increase in diameter of 55±9% (mean±SEM) at 4 hours. Coapplication of either NS-398 or dexamethasone with LPS reduced dilatation of cerebral arterioles at hours 2 through 4 (P<0.05). In contrast, NS-398 did not inhibit dilatation of cerebral arterioles in response to bradykinin or ADP. In animals injected intracisternally with vehicle, COX-2 protein was expressed at a very low level in leptomeningeal tissue. Intracisternal injection of LPS increased COX-2 protein expression by approximately 20-fold (P<0.05). In leptomeningeal tissue treated ex vivo with LPS, there was also expression of COX-2. Both dexamethasone and NS-398 markedly reduced COX-2 protein expression in ex vivo LPS-treated tissue. PGE2 production was detectable under control conditions in leptomeningeal tissue incubated in vehicle ex vivo for 4 hours (6.5±1.1 pmol/mg protein). LPS treatment significantly increased PGE2 production to 12.8±1.1 pmol/mg protein (P<0.05). Both dexamethasone and NS-398 significantly attenuated LPS-induced PGE2 production (P<0.05).

Conclusions—LPS increased expression of COX-2 protein in leptomeningeal tissue and caused COX-2–dependent dilatation of cerebral arterioles in vivo. Ex vivo, both NS-398 and dexamethasone suppressed LPS-induced PGE2 production and COX-2 expression in leptomeningeal tissue. Inhibition of LPS-induced dilatation of cerebral arterioles in vivo by NS-398 and dexamethasone suggests that the dilatation was dependent on expression and activity of COX-2. These findings support the concept that exposure of brain to LPS causes cerebral vasodilatation that is dependent in part on expression and activity of COX-2. (Stroke. 1998;29:2600-2606.)

Key Words: cerebral arteries ■ cyclooxygenase ■ dexamethasone ■ lipopolysaccharides ■ vasodilation

Cyclooxygenase is the rate-limiting enzyme in the production of prostaglandins, converting arachidonic acid to prostaglandin H2 (PGH2). Many tissues express a constitutive isoform of cyclooxygenase (COX-1) under normal conditions. A second isoform of cyclooxygenase (COX-2) has been described. In most cultured cells, COX-2 is not expressed under normal conditions, but inflammatory stimuli, including lipopolysaccharide (LPS), reactive oxygen species, and some cytokines and growth factors, can upregulate COX-2 expression. Expression of COX-2 leads to increased production of prostanooids. In brain, prostanooids are potent vasoactive and inflammatory substances. In brain of adult animals, a subpopulation of neurons normally expresses COX-2. Other brain cells, including microglia,

See Editorial Comment, page 2606
astrocytes, and vascular cells, do not normally express significant levels of COX-2 but upregulate COX-2 expression after inflammatory stimuli. In addition, certain pathophysiological conditions, including ischemia and hypoxia, are associated with increased expression of COX-2 in brain.

We and others have shown that indomethacin can partially inhibit LPS-induced dilatation of cerebral arterioles and increased cerebral blood flow. Because indomethacin inhibits activity of both COX-1 and COX-2, it is not known which isoform of COX is responsible for LPS-induced cerebral vasodilatation. In the present study we examined the hypothesis that exposure of the cerebral cortex to LPS would cause expression of COX-2 and dilatation of cerebral arterioles. We further hypothesized that LPS-induced dilatation of cerebral arterioles would be inhibited by dexamethasone, which prevents expression of COX-2 and NS-398, a selective inhibitor of COX-2 enzymatic activity.

Materials and Methods

Cranial Windows

Male Sprague-Dawley rats (n=4; weight, 341±3 g) were anesthetized with pentobarbital (50 mg/kg IP). A tracheostomy was performed, and ventilation was maintained with a small-animal ventilator. Paco2 was adjusted to 40 mm Hg by altering minute ventilation, and PaO2 was maintained at >100 mm Hg by supplementing room air with oxygen. Anesthesia was supplemented by administration of additional pentobarbital (5 to 15 mg/kg per hour) through the femoral vein. Rectal temperature was measured and maintained at 37±0.5°C with a heating pad.

A closed cranial window was prepared in a manner similar to that described in rabbits. The scalp, muscle, and periostium overlying the parietal area of the skull were reflected, and bleeding was controlled with bone wax. The dura overlying an arteriole was incised. Two blunt needles were affixed to a dam of dental acrylic. An outlet tube was affixed to one needle and set to (12 mm) was fused to the wax. The window was reinforced with bone wax surrounding the craniotomy, and a circular glass coverslip was placed over the cranial window.

Arteriolar diameter was measured with a calibrated video micrometer. The preparation was allowed to equilibrate for 30 minutes, during which time the window was flushed with 2 mL of aCSF every 30 minutes, for 4 hours. After recovery, cranial windows were flushed with aCSF containing NS-398 (100 μmol/L) for 4 hours. Dilatation to ADP (10-6 and 10-3 mol/L) was then retested in the presence of NS-398 (100 μmol/L). In the second group of animals (n=6), dilatation to bradykinin (10-6, 10-3 mol/L) was tested, and cranial windows were then flushed with NS-398 (100 μmol/L) every 30 minutes for 4 hours. Dilatation to bradykinin was then retested in the presence of NS-398 (100 μmol/L). Bradykinin causes an immediate, reversible dilatation in cerebral arterioles that is dependent on cyclooxygenase (presumably COX-1, since the time course and reversibility of the bradykinin-dependent dilatation are not consistent with COX-2 expression and activity).

Intracisternal Injection

In a separate group of rats (n=7), expression of COX-2 protein was determined by Western blot analysis. Preliminary studies demonstrated that harvesting brain directly beneath the cranial window did not yield sufficient tissue to allow adequate protein for Western blot analysis. To circumvent this problem, intracisternal injection of LPS was performed to expose the entire brain surface to LPS. The amount of LPS injected (40 ng) was calculated on the basis of the estimated cerebrospinal fluid (CSF) volume in an adult rat (300 to 400 μL) to yield a concentration of LPS equivalent to that used in the cranial window experiments (100 ng/mL). The concentration of LPS in CSF produced with this procedure is probably less than the total dose delivered in cranial windows because the windows were flushed with LPS-containing CSF every 30 minutes for 4 hours.

For intracisternal injections, rats were anesthetized with pentobarbital (50 mg/kg IP) and atropine (15 μg/kg IP) to inhibit respiratory secretions. During the course of the procedure, the pentobarbital was supplemented as needed (5 to 15 mg/kg per hour) to maintain an adequate level of anesthesia. Animals were placed in a stereotactic head frame, and the atlanto-occipital membrane was exposed through a small incision. The atlanto-occipital membrane was punctured with a 27-gauge needle in a stereotaxic arm and confirmed by aspiration of CSF. After aspiration of 100 μL of CSF, 100 μL of aCSF (with or without LPS, 40 ng) was injected over 15 minutes.

For Western Blot Analysis

Animals were killed with an overdose of pentobarbital, the brain was rapidly removed, and the leptomeninges containing pial blood vessels were separated from the cortex. The surface was kept moist with ice-cold phosphate-buffered saline, the meninges were incised and peeled from the surface with fine-tipped forceps under a dissecting microscope. Portions of meninges were removed as intact sheets of tissue. The isolated leptomeninges were homogenized by sonication in ice-cold lysis buffer (50 mmol/L Tris, pH 7.5, 150 mmol/L NaCl, 100 μmol/L phenylmethylsulfonyl fluoride, 1 μg/mL aprotinin, 1 μg/mL leupeptin, 1 mmol/L diethyl-dithiocarbamic acid, 1% Nonidet P-40, and 1% sodium deoxycholate), and protein content was determined. Equal amounts of protein per lane (100 μg) were loaded onto a 7.5% polyacrylamide gel and separated by electrophoresis at 200 V for 45 minutes. Proteins were then transferred to nitrocellulose at 100 V for 1 hour, and the membrane was blocked with 5% nonfat dry milk at 0.5% Tween-20 in Tris-buffered saline. The nitrocellulose was then cut and developed.
incubated with a rabbit polyclonal antibody specific for COX-2 (Cayman Chemical, catalog No. 160106; 1:1000) overnight at 25°C followed by horseradish peroxidase–conjugated secondary antibodies (donkey anti-rabbit, Amersham) for 1 hour at 25°C. Antibody labeling was detected by chemiluminescence (Pierce). To verify antibody specificity and the size of the COX-2 bands, protein extracts from cultured, cytokine-activated RAW 264.7 macrophages were used as controls for COX-2. Color molecular weight standards were also run on each gel. Western blot results were quantified by densitometry.

**Ex Vivo Leptomeningeal Treatment**

Rats (n=8) were anesthetized with ether and decapitated. Leptomeningeal tissue was removed as described above. In each animal, tissue from each hemisphere was used as a single sample. Each treatment group contained leptomeningeal tissue from 4 different rats. Control leptomeningeal tissue was placed immediately after dissection in ice-cold lysis buffer for protein determination and analysis of COX-2 expression by Western blot. Experimental samples were placed into serum-free Dulbecco’s modified Eagle’s medium (DMEM) with or without LPS (100 ng/mL), LPS and dexamethasone (1 μmol/L), or LPS and NS-398 (100 μmol/L). When meninges were harvested for NS-398 or dexamethasone treatment, the buffer to moisten brains during harvesting contained appropriate concentrations of NS-398 or dexamethasone. Tissue was incubated at 37°C for 4 hours, and the media was removed and analyzed for prostaglandin E_2 (PGE_2) concentration. Tissue was homogenized for protein determination and analysis of COX-2 (PGE_2) concentration. Tissue was homogenized for protein determination and analysis of COX-2 expression by Western blot analysis. PGE_2 was quantified by radioimmunoassay with the use of an antibody specific for PGE_2 (Seragen). Cross-reactivity of this antibody with other eicosanoids is <0.1%. Prostaglandin production was normalized to protein content of each sample.

**Statistical Analysis**

Data are expressed as mean±SEM. Data between groups were compared by ANOVA and Duncan’s post hoc test. Data within groups were analyzed by repeated-measures ANOVA and post hoc comparison by means contrast. P<0.05 was considered significant.

**Results**

**Effect of NS-398 on LPS-Induced Dilatation of Cerebral Arterioles**

Baseline arteriolar diameter was not different between groups and averaged 53±1 μm. Dilatation of cerebral arterioles in response to ADP (10⁻⁵, 10⁻⁴ mol/L) performed at the beginning of each study averaged 8±1% and 17±1%, respectively.

In control animals treated with aCSF (n=5), there was no change in arteriolar diameter over the 4 hours of study (P>0.05; Figure 1A). In contrast, LPS (n=8; 100 ng/mL) caused time-dependent dilatation of cerebral arterioles, reaching 55±9% at 4 hours (Figure 1A). LPS-induced changes in arteriolar diameter were significantly different than those in the aCSF group at hours 2 to 4 (P<0.05). When NS-398 (n=8; 100 μmol/L) was coapplied with LPS, vasodilatation was significantly reduced at hours 2 to 4 (Figure 1B; P<0.05). Coaplication of dexamethasone (n=5; 1 μmol/L) with LPS also attenuated LPS-induced vasodilatation at hours 2 to 4 (Figure 1B; P<0.05). There were no differences either across time or between groups in mean arterial pressure or arterial blood gas values, which averaged 125±1 mm Hg, pH 7.39±0.003, Paco_2 40±0.3 mm Hg, and Pao_2 205±2 mm Hg, respectively (P>0.05).

**Effect of NS-398 on Bradykinin- and ADP-Induced Dilatation of Cerebral Arterioles**

In separate groups of animals, there were no significant differences (P>0.05) in arteriolar diameter, mean arterial pressure, or arterial blood gases, which averaged 52±2 μm, 128±1 mm Hg, pH 7.40±0.003, Paco_2 40±0.3 mm Hg, and Pao_2 206±3 mm Hg, respectively. In LPS-injected rats (n=6), bradykinin (10⁻⁶, 10⁻⁵ mol/L) produced vasodilatation that was not significantly affected (P>0.05) by treatment with NS-398 (100 μmol/L) every 30 minutes for 4 hours (Figure 2A). In a second group of animals (n=3), vasodilatation to bradykinin (10⁻⁶, 10⁻⁵ mol/L) was similar (P>0.05) before (18±7%; 40±8%) or after (21±9%; 38±9%) flushing windows with aCSF every 30 minutes for 4 hours. In a third group of animals (n=6), vasodilatation to ADP (10⁻⁵, 10⁻⁴ mol/L) was not significantly different (P>0.05) before or after treatment with NS-398 (100 μmol/L) every 30 minutes for 4 hours (Figure 2B).

**LPS-Induced COX-2 Expression In Vivo**

In animals injected intracisternally with vehicle (n=3), COX-2 expression in leptomeningeal tissue was slight but detectable by Western blot analysis (Figure 3). Intracisternal injection of LPS markedly increased COX-2 protein expression in leptomeningeal tissue (~20-fold; n=4; Figure 3).

**LPS-Induced COX-2 Expression and PGE_2 Production Ex Vivo**

In freshly harvested leptomeningeal tissue, there was no detectable COX-2 protein expression by Western blot (n=4; Figure 4A). Incubation of leptomeningeal tissue ex vivo with media for 4 hours induced expression of COX-2 (n=4; Figure 4B). Bradykinin caused dose-dependent dilatation (10⁻⁶ mol/L [filled bars], 10⁻⁵ mol/L [open bars]) under control conditions. After treatment of cranial windows every 30 minutes for 4 hours with NS-398 (100 μmol/L), dilatation to bradykinin was not different (P>0.05). ADP produced dose-dependent dilatation (10⁻⁶ mol/L [filled bars], 10⁻⁵ mol/L [open bars]) under control conditions. After treatment of cranial windows every 30 minutes for 4 hours with NS-398 (100 μmol/L), dilatation to ADP was not different (P>0.05). Data are mean±SEM.
LPS treatment (100 ng/mL; n = 4) of leptomeningeal tissue caused an additional increase in COX-2 protein expression (n = 4; Figure 4A), which was significantly reduced (P < 0.05) by dexamethasone (1 μmol/L/ml; n = 4) or NS-398 (100 μmol/L/ml; n = 4; Figure 4B).

In leptomeningeal tissue incubated ex vivo with LPS, PGE2 production approximately doubled compared with incubation with media (P < 0.05; Figure 4C). Dexamethasone and NS-398 both prevented LPS-induced increase in PGE2 (Figure 4C).

**Discussion**

There are several new findings in this study. First, LPS produced time-dependent dilatation of cerebral arterioles in vivo that was inhibited by NS-398 and dexamethasone. Second, NS-398 appears to be a relatively selective inhibitor of COX-2 in brain in vivo. Third, direct application of LPS to brain cortical surface caused significant upregulation of COX-2 protein expression in leptomeningeal tissue. Fourth, exposure of ex vivo leptomeningeal tissue to LPS upregulated COX-2 protein expression and PGE2 production. Both dexamethasone and NS-398 suppressed COX-2 expression and PGE2 production ex vivo. Data from ex vivo experiments are consistent with in vivo data demonstrating COX-2–dependent dilatation of cerebral arterioles and expression of COX-2 protein after treatment with LPS. Because LPS-induced dilatation in brain was significantly reduced by both NS-398 and dexamethasone, these findings support the concept that LPS-induced cerebral vasodilatation is dependent in part on expression and activity of COX-2.

**COX-2 Expression in Brain**

COX-2 is an inducible isoform of cyclooxygenase, distinct from the constitutive form, COX-1.1 In most tissues, COX-2 is not expressed under basal conditions but is upregulated by certain factors, including inflammatory stimuli.1–6 Once expressed, COX-2 increases production of prostaglandins.1 The principal prostaglandin produced during inflammation is PGE2,1 and PGE2 is a potent dilator of cerebral blood vessels.7 Cyclooxygenase can also produce reactive oxygen species, which are vasodilators in brain.24

In brain, a number of cell types can express COX-2 during inflammatory conditions in vitro. Cultured astrocytes, microglia, and microvascular cells (both endothelium and smooth muscle) express COX-2 and increase prostanoid production after stimulation with LPS or cytokines.11,27–29 In vivo, intravenous LPS or cytokines cause expression of COX-2 in the cerebral endothelium, vascular, perivascular, and leptomeningeal cells.12,20,31 In the present study we did not identify the specific cells expressing COX-2 but rather documented LPS-induced expression of COX-2 protein in leptomeningeal tissue by Western blot.

In the present study we detected minimal expression of COX-2 protein in leptomeningeal tissue after intracisternal injection of aCSF (Figure 3) and in freshly harvested leptomeningeal tissue (Figure 4A). The leptomeningeal tissue consists principally of the arachnoid and pial layers of the meninges and the accompanying vascular structures. There may be slight contamination with underlying superficial brain tissue, which contains primarily glial cells. We believe that it is unlikely that the leptomeningeal preparation included neurons that constitutively express COX-2 because these
neurons are found in deeper brain structures. Furthermore, when we analyzed freshly harvested leptomeningeal tissue from animals that had not undergone intracisternal injection, we did not detect COX-2 protein. It is likely that a mild inflammatory reaction occurred after intracisternal injection of aCSF. We prepared the aCSF under sterile conditions and used sterile, disposable supplies when performing intracisternal injections. Low levels of LPS could be present in the aCSF, which could account for the minimal COX-2 expression in animals injected with aCSF. However, intracisternal injection of LPS (40 ng) increased COX-2 expression in leptomeningeal tissue in vivo by 20-fold.

Leptomeningeal tissue from animals that had not undergone intracisternal injection did not express COX-2. However, incubation of leptomeningeal tissue in DMEM for 4 hours caused expression of COX-2. We used sterile supplies and endotoxin-free reagents for the incubation but cannot completely rule out LPS contamination as a causative factor for COX-2 expression. It is also possible that the process of stripping the leptomeningeal tissue from the brain could activate mechanisms, resulting in expression of COX-2. As in vivo, LPS treatment of leptomeningeal tissue ex vivo caused an additional increase in COX-2 protein expression, which was attenuated by both dexamethasone and NS-398. In cultured microglia, PGE2 and cAMP have a positive effect on COX-2 expression. Consistent with this, the promoter region of the COX-2 gene contains a cAMP response element. Because NS-398 inhibits prostanoid production from COX-2, it is possible that NS-398 attenuated COX-2 expression in ex vivo leptomeningeal tissue by reducing prostanoid and cAMP production.

Dexamethasone suppresses LPS or cytokine-induced expression of COX-2 in cultured astrocytes, microglia, and cerebrovascular cells. The COX-2 gene lacks a glucocorticoid response element by which dexamethasone could suppress COX-2 expression. However, dexamethasone may suppress expression of COX-2 by other mechanisms, including direct inhibition of the transcription factors activator protein-1 and nuclear factor-κB. Both activator protein-1 and nuclear factor-κB bind to the promoter region of COX-2, activating COX-2 transcription. Although we did not study the mechanism by which dexamethasone prevented LPS-induced dilatation, there is good evidence that dexamethasone suppresses expression of COX-2.

Dexamethasone appears to have minimal, if any, direct vascular effects. We have previously reported that prolonged exposure of cerebral arterioles in vivo to dexamethasone does not alter resting diameter. Furthermore, dexamethasone does not inhibit ADP-mediated dilatation of cerebral arterioles (which is NO dependent). Others have reported that dexamethasone does not alter constrictor or dilator responses of cerebral and extracerebral vessels. Dexamethasone does not affect the activity of COX-1 in vivo. Thus, it is unlikely that dexamethasone reduced LPS-induced dilatation by a nonspecific effect on vascular tone.

We have previously reported that dexamethasone and indomethacin inhibited LPS-induced dilatation of cerebral arterioles in rabbits. In both the previous and present studies, dexamethasone tended to produce more suppression of LPS-induced dilatation than indomethacin or NS-398, although this was not statistically significant. LPS can also cause expression of inducible NO synthase, which is inhibited by dexamethasone. Thus, dexamethasone could produce a greater reduction of LPS-induced dilatation because of suppression of both inducible NO synthase and COX-2 expression. On the basis of the present data, we cannot comment on the relative contribution of COX-2 versus inducible NO synthase to the observed dilatation. Our findings also do not exclude potential interaction of inducible NO synthase and COX-2. We used NS-398 and dexamethasone as pharmacological tools to demonstrate involvement of the specific systems under study.

**NS-398 and COX-2**

NS-398 has been reported to be a selective inhibitor of COX-2 enzymatic activity. In vitro, NS-398 in concentrations up to 100 μmol/L does not inhibit activity of COX-1 in isolated enzyme preparations. In vivo, NS-398 does not reduce COX-1 activity in gastric tissue, even when there is complete suppression of COX-2 activity in inflammatory exudates. In the present study bradykinin caused dose-dependent dilatation of cerebral arterioles, which was not significantly inhibited by NS-398. The specific isof orm of COX activated by bradykinin has not been definitely identified but is most likely COX-1, since acute application of bradykinin caused immediate, reversible dilatation of cerebral arterioles, which can be blocked with indomethacin. This time course is not consistent with bradykinin causing expression of COX-2 with subsequent dilatation. In addition, bradykinin-induced dilatation of cerebral arterioles is endothelium dependent, and it appears unlikely that COX-2 is expressed in cerebral vessels of adult animals under normal conditions. NS-398 also did not affect dilatation of cerebral arterioles due to activation of endothelial NO synthase with ADP. Our data suggest that NS-398 is selective for COX-2 in brain in vivo and that the inhibitory effect of NS-398 on LPS-induced dilatation is due to inhibition of COX-2 activity. We have previously reported that in rabbit cerebral arterioles in vivo, indomethacin reduced LPS-induced dilatation by ~50%, which is consistent with the findings of the present study.

In summary, we have demonstrated that topical application of LPS caused marked, time-dependent dilatation of cerebral arterioles that was inhibited by NS-398, a selective inhibitor of COX-2, as well as dexamethasone. We documented LPS-mediated increased expression of COX-2 protein in leptomeningeal tissue in vivo and ex vivo by Western blot analysis, consistent with our pharmacological data that COX-2 contributes to LPS-induced dilatation of cerebral arterioles in vivo. We also demonstrated COX-2–dependent PGE2 production in LPS-treated leptomeningeal tissue ex vivo. These data suggest that expression and activity of COX-2 are important components of the vascular response to inflammation in brain in vivo. While this report was under revision, another study was published which also suggests that expression of COX-2 contributes to cerebral vasodilatation after treatment with LPS.
Acknowledgments

This study was supported by National Institutes of Health grants NS-24621 and HL-38901, by American Heart Association Grant-in-Aid 96 50661N, and by research funds from the Department of Anesthesia, University of Iowa College of Medicine. Dr Fracar is an Established Investigator of the American Heart Association. The authors wish to express thanks to Paula Ludwig and Elizabeth Yoder for technical assistance.

References

Prostaglandins are involved in the regulation of a wide variety of normal and pathophysiological biological functions, including inflammation.1 It has recently been recognized that the inducible form of cyclooxygenase (COX-2) plays a central role in the induction and amplification of inflammation.2

The above article as well as that of Okamoto et al,3 published earlier in Stroke, confirm the crucial role of COX-2 in the induction of vasodilation, one of the cardinal manifestations of inflammation in the brain. In both studies the inflammatory reaction was induced by the administration of lipopolysaccharide, an endotoxin product. It was demonstrated that COX-2 was induced, its activity increased with resulting increased production of prostaglandins, and the inhibition of the induction of the enzyme or inhibition of its activity resulted in a reduction in vasodilation.

There are significant practical benefits from the use of agents that inhibit either the induction or the activity of COX-2 in preventing the adverse consequences of inflammation of the brain. The inflammatory process in the brain causes, in addition to vasodilation, edema and, ultimately, neuronal dysfunction. Inhibition of the process is very likely to minimize or prevent the consequent brain dysfunction. The confirmation, therefore, that COX-2 plays an important role in the inflammation of the brain constitutes a significant advance.

Hermes A. Kontos, MD, PhD
Associate Editor for Basic Science
Virginia Commonwealth University
Medical College of Virginia Campus
Richmond, Virginia

References
Expression and Vascular Effects of Cyclooxygenase-2 in Brain
Johnny E. Brian, Jr, Steven A. Moore and Frank M. Faraci

Stroke. 1998;29:2600-2606
doi: 10.1161/01.STR.29.12.2600
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/29/12/2600

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/