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Prolonged opportunity for neuroprotection in experimental stroke with selective blockade of cyclooxygenase-2 activity

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Abstract

The post-treatment effects of the selective cyclooxygenase (COX)-2 inhibitor, valdecoxib, were investigated in a rat model of temporary focal ischemia. Valdecoxib reduced basal brain prostaglandin E₂ concentrations at dosages that did not affect serum thromboxane B₂, consistent with a selective COX-2 effect. Temporary focal cerebral ischemia was produced in rats by middle cerebral artery occlusion for 90 min. There was increased expression of COX-2 protein detected by Western blot and immunocytochemistry within neurons in the ischemic cortex at 4 and 24 h after ischemia. Rats were treated with vehicle or valdecoxib 15 min before or 1.5, 3 and 6 h after cerebral ischemia. Rats were sacrificed and brain infarction volume determined 24 h after ischemia. Valdecoxib treatment was associated with a decrease in infarction volume when administered 15 min before, and 1.5 or 3 h but not 6 h after cerebral ischemia. There were no differences in physiological parameters during the procedure. Valdecoxib administered at 1.5 h after ischemia significantly reduced the concentrations of prostaglandin E₂ in ischemic penumbral cortex as compared to the vehicle-treated group and contralateral non-ischemic cortex. These results suggest that COX-2 inhibition with valdecoxib is effective when initiated both before and after middle cerebral artery occlusion.

Keywords

cerebral ischemia; therapeutic window; Clinical significance; valdecoxib; COX-2 inhibitor

1. Introduction

Cyclooxygenases are responsible for metabolic breakdown of arachidonic acid into prostaglandin (PG)s that have been reported to have both pro- and anti-inflammatory roles in mammalian systems besides serving other physiological functions. COX-1 and COX-2, the two major isoforms of cyclooxygenases, share the same catalytic functions but have different physiologic roles. COX-1 is present in most cells constitutively and is involved in normal housekeeping functions. COX-2 is the predominant isoform expressed in neurons and its expression is induced by excitatory amino acids and spreading depression, two mechanisms

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that have been proposed to exacerbate ischemic neuronal injury (Kaufmann et al., 1996; Miettinen et al., 1997; Yamagata et al., 1993).

There is strong evidence suggesting a prominent role for COX-2 in cerebral ischemic injury (Candelario-Jalil and Fiebich, 2008; del Zoppo et al., 2000; Minghetti, 2007). Disruption of the COX-2 gene provides protection against ischemic brain injury in rodents (Candelario-Jalil and Fiebich, 2008; Iadecola et al., 2001) while COX-2 over-expressing mice have larger infarcts after experimental stroke (Dore et al., 2003). Additionally, selective pharmacologic inhibition of COX-2 activity has proven to be a potential therapeutic target against stroke in animal models (Nakayama et al., 1998; Nogawa et al., 1997a).

The present study was carried out to investigate the pre- and post-stroke effects of the water soluble, orally administered COX-2 inhibitor valdecoxib in temporary focal ischemia.

2. Methods

All work was done with approval of the University of Pittsburgh Institutional Animal Care and Use Committee.

2.1. Middle Cerebral Artery Occlusion (MCAO) and assessment of Infarction Volume

MCAO surgery and measurement of infarction volume was performed as described earlier (Poloyac et al., 2006). Rats were intubated using a 14G catheter and maintained with 2% isoflurane, 70/30 N₂O/O₂ throughout surgery. The left common carotid artery (CCA) was exposed and the external common carotid artery was isolated and ligated using 5-0 silk (Ethicon). MCAO was achieved by inserting 4-0 nylon suture (with tip coated with silicon 1.5 – 2.0 mm diameter) into the internal carotid artery (ICA) a distance of 1.5 cm from the bifurcation of the CCA and ICA. The wound was closed and the animals were allowed to recover with the suture in place. After 90 min. the rat were re-anesthetized and the suture removed, initiating reperfusion. Sham surgeries were performed in the same manner as MCAO surgeries but without insertion of suture. Occlusion of the MCA by the filament and reperfusion on its withdrawal was confirmed by using laser Doppler flowmetry (Perimed, Jarfalla, Sweden). 24 h after reperfusion, rats were sacrificed and their brains were harvested. Throughout the surgical procedure and until 1h after reperfusion, rectal temperature was maintained in the range of 37 – 38 °C using a thermoregulated heating pad and heating lamp. The brains were then sliced into 2 mm thick sections and stained with 3% TTC (2, 3, 5-triphenyl tetrazolium chloride), (Sigma, St. Louis, MO) at 37°C for 15 min. Sections were then fixed in 4% paraformaldehyde overnight and then photographed and infarct volumes measured using MCID (St. Catharines, ON). Physiological parameters were monitored in a separate cohort of rats (n=6 per group). Arterial blood samples collected via femoral catheter were analyzed for blood gasses before the occlusion and during occlusion. Arterial blood pressure was measured before the occlusion and during occlusion.

2.2. Western Blot

Rats (n=3 per group) underwent Sham or MCAO surgeries as described above and were sacrificed at 24 h after reperfusion. Ipsilateral and contralateral penumbral cortices were homogenized with T-PER (tissue protein extraction reagent) plus protease inhibitors (Pierce, Rockford, IL) and proteins measured. Equal amounts of sample proteins were subjected to SDS-PAGE, and COX-2 levels were detected using a polyclonal anti-COX-2 antibody (1:2000; Cayman Chemical, Ann Arbor, MI). Blots were stripped and reprobed with β -actin antibody (1:8000; Sigma, St. Louis, MO) to confirm equal protein loading. Results were quantified using MCID.

2.3. Immunohistochemistry

Brains (n=3 per group) were perfusion fixed with formalin via the left ventricle, then placed in 15% sucrose 24 h after immersion in formalin. After sinking, brains were moved to 30% sucrose for 48 hours, and then cut into 3mm sections and paraffin embedded. Blocks were cut in 5 μ m sections and mounted on gelatinized slides. Slides were deparaffinized and stained for NeuN (1:200; Chemicon, Mab377) and COX-2 (1:400; Cayman Chemical 160126). Secondary antibodies (goat anti-rabbit Cy3, 1:200, for COX-2 and goat anti-mouse AlexaFluor 488, 1:200, for NeuN) were applied for 1 h at room temperature then coverslipped. Photos were taken with an Olympus Fluoview Confocal microscope at 10 and 240X.

2.4. Valdecoxib treatment

Male Sprague Dawley rats, 280 – 300 g were treated orally, via gastric lavage, with valdecoxib or water (vehicle). For dose response experiments, animals (n=3 per group) received vehicle or valdecoxib 0.001 – 10 mg/Kg and for MCAO experiments animals received 1 mg/Kg, via gastric lavage at 15 min pre- MCAO, 1.5, 3 or 6 h post onset MCAO (1.5 h post onset for vehicle). For all other experiments rats were treated 90 min post onset MCAO.

2.5. Prostaglandin E₂ and Serum Thromboxane B₂ measurement

After 24 h of reperfusion, the rats were sacrificed and penumbral cortices (n=8 per group) dissected and rapidly frozen in liquid nitrogen. Tissue was homogenized in ice cold 30% MeOH, 70% 0.05M Tris HCl, centrifuged and supernatant collected and dried. PGE₂ was measured following manufacturer's directions (Cayman Chemical, Ann Arbor, MI). For valdecoxib dose response studies, hippocampi were used (n=3 per group). Blood was drawn at sacrifice and serum thromboxane B₂ (TXB₂) measured following manufacturer's directions (Cayman Chemical).

2.6 Statistical Analysis

Data were analyzed using one-way ANOVA followed by student's T-test to calculate the difference between groups. Significance level was set at $p < 0.05$.

3. Results

3.1. COX-2 expression after cerebral ischemia

Immunohistochemical staining of penumbral cortices exhibited significant expression of COX-2 24 h after temporary focal ischemia, co-localizing with Neu-N, a neuronal marker (Fig 1 A). Western blot analysis of penumbral cortical tissue for COX-2 protein showed increased ipsilateral expression relative to weak bands, corresponding to basal levels of COX-2 protein, in contralateral tissue after 4 h and 24 h of reperfusion (Fig 1B). Densitometric analysis indicates an increase in COX-2 expression in ipsilateral as compared to contralateral cortical brain tissue (Fig 1C). These results indicate that COX-2 protein is increased after temporary focal ischemia, consistent with a possible role for COX-2 as a delayed mediator of ischemic injury in neurons.

3.2. Valdecoxib dose selectively

The valdecoxib dose-response curve (Fig 2) shows that at doses ranging from 0.001 – 10.0 mg / Kg, valdecoxib significantly lowered the basal production of endogenous PGE₂ in naive rat hippocampi 3 h after treatment. There was no significant effect upon serum TXB₂, a COX-1 coupled prostaglandin product, at doses of less than 10 mg/kg. Thus, 1 mg / Kg was chosen for subsequent studies since it produced maximal effects on PGE₂ brain concentrations, but had little effect upon serum TXB₂, suggesting that valdecoxib is COX2-selective at this dose.

3.3. Effect of valdecoxib on infarction volume after cerebral ischemia

Rats treated with valdecoxib 15 min before MCAO, 1.5 and 3h after reperfusion showed significant reduction in infarction volume; however no statistically significant effect was found in the 6h post-treatment group (Figure 3 A&B). In a separate cohort of animals, relative cortical blood flow as measured by laser Doppler flowmetry 5 min before MCAO, 10 min after MCAO, 5 min and 4 h after reperfusion did not differ significantly between vehicle and valdecoxib groups; however, there was a significant difference in relative cortical blood flow between pre-MCAO and post-MCAO time points for both the groups (Table 1). Physiological parameters were not different between the two groups before or after MCAO (Table 2 A). Similarly, there were no significant differences in core body temperature or mean arterial blood pressure before, during or after occlusion. (Table 2 B & C)

3.4. Effect of valdecoxib on PGE₂ production in brain

There was a highly significant increase in the endogenous production of PGE₂ in ipsilateral as compared to contralateral cortex after MCAO in the vehicle treated group. Post-treatment with valdecoxib normalized the ipsilateral PGE₂ levels significantly as compared to vehicle treatment (Figure 4). The contralateral PGE₂ levels remained unchanged for both groups.

4. Discussion

COX-2 protein expression in neurons is induced by cell excitation and spreading depression, events that occur as a result of the release of excitatory amino acids after ischemia. Thus, expression and activation of COX-2 may be an important delayed mechanism of neuronal injury after ischemia. In this study there was increased expression of COX-2 protein at 4 and 24 h after temporary focal ischemia. Previous studies (Miettinen et al., 1997; Nogawa et al., 1997b; Planas et al., 1995) have also reported increased expression of COX-2 in ipsilateral hemisphere of rat brain after MCAO. This expression was localized to ipsilateral cortical areas and was evident as early as 30 min and persisted to, at least, 24 h after ischemia. These results suggest that COX-2 activity may mediate delayed injury after ischemia. In the current study, pre- and post-treatment with valdecoxib significantly reduced brain infarction volume after cerebral ischemia. Other studies have also shown that post-treatment with COX-2 inhibitors hours after ischemia can reduce ischemic injury (Candelario-Jalil et al., 2004; Candelario-Jalil et al., 2007; Hara et al., 1998; Iadecola et al., 2001; Nogawa et al., 1997b; Sugimoto and Iadecola, 2003). This relatively long treatment window after the onset of ischemia during which COX-2 inhibitors are still effective suggests that COX-2 inhibition could be a practical treatment in human stroke.

In the current study, treatment with the COX-2 inhibitor valdecoxib prevents increases in brain concentrations of PGE₂. PGE₂ elicits its detrimental effects in cerebral ischemia and excitotoxicity by activating its EP1 receptor subtype. Selective blockade or genetic ablation of the EP1 receptor in mice abrogated neuronal damage caused by cerebral ischemia or excitotoxicity (Ahmad et al., 2006a; Kawano et al., 2006). EP1 receptors are G Protein-coupled receptors that have the capability to inhibit intracellular cAMP levels and increase loads of intracellular calcium (Dore, 2006; Hata and Breyer, 2004; Sugimoto and Narumiya, 2007). Release of intracellular calcium is reported to play a major role in neuronal injury induced by cerebral ischemia in animal models (Lipton, 1999), whereas enhancers of intracellular levels of cAMP have been suggested to be protective in cellular models of ischemia or excitotoxicity (Ahmad et al., 2006b; McCullough et al., 2004). Thus neuronal protection in the present studies might have, at least, in part been executed by the inhibition of enhanced PGE₂ synthesis and therefore it's binding to harmful EP1. COX-2 may also control the production of other prostaglandins such as PGD₂, PGI₂ and PGF_{2a} which may have a variety of protective and/or injurious effects in cerebral ischemia.

In the current study, valdecoxib treatment resulted in smaller infarct volumes after 90 min. of MCA occlusion compared to treatment with vehicle controls, even when the drug was administered 90 min after the suture was removed. Since removing the suture 90 min. or later after insertion does not prevent infarction of the entire MCA distribution (Longa et al., 1989), treatment with valdecoxib extends the time window during which reperfusion by suture removal is effective in reducing infarction volume in this model. These data and the lack of an effect of COX-2 inhibitors upon platelet function (Graff et al., 2007; Spektor and Fuster, 2005) suggest that drugs such as valdecoxib could be useful adjuncts to thrombolytic therapy. However, the current studies do not model many of the other effects of thrombolytic drugs such as tissue plasminogen activating factor, so further studies in additional models are required to test whether COX-2 inhibition synergistically extends the time window during which thrombolysis is beneficial.

There are a number of other limitations to the current study. The dose response data for brain PGE₂ concentrations in naïve animals may not exactly correspond to dose response of the drug in ischemic brain. Thus the most effective dose of valdecoxib may not have been used for these studies. Behavioral outcome data was not collected in this study, and such data is necessary to select candidate drugs for clinical translation. These limitations of the data will require additional studies to address. Despite these limitations, the current results add to the body of literature that demonstrate that COX-2 inhibitors improve behavioral and histological outcome in transient focal ischemia models, even when COX-2 inhibition is initiated hours after ischemia.

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Abbreviations

COX, Cyclooxygenase; PG, prostaglandin; TX, thromboxane; MCAO, middle cerebral artery occlusion; CCA, common carotid artery; ICA, internal carotid artery.

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Figure 1.

Expression of COX-2 in penumbral cortical tissue 24h after cerebral ischemia. (A) Confocal images of immunostained sections of ischemic cortex stained with Dapi (blue) to detect nuclei, antiNeu-N antibody (green) to detect neurons and antiCOX-2 antibody (green) to detect COX-2 expression. (B) Immunoblot detecting COX-2 protein 4h and 24h of cerebral ischemia and corresponding (C). Graph summarizing densitometric analysis of COX-2 expression. n=3. Ipsi or I: ipsilateral. Contra and C: contralateral.

Figure 2.

Effect of valdecoxib on hippocampal prostaglandin E₂ and serum thromboxane B₂ concentrations in naïve rats. Rats received 0.001 – 10.0 mg/Kg. Valdecoxib or vehicle via gastric lavage and were sacrificed 3h later. n = 3 per group. Ipsi: ipsilateral; contra: contralateral.

Figure 3. Effect of valdecoxib pre- and post-treatment Infarction volume in rats after induction of cerebral ischemia. Representative TTC-stained sections showing reduction infarct volumes and B) Graphic representation of reduction in % corrected infarction volume. ** $P < 0.001$; * $P < 0.05$ vs vehicle. $n = 6$ per group.

Figure 4.

Effect of valdecoxib post-treatment on PGE₂ production in penumbral cortex after cerebral ischemia. Rats were treated with vehicle or valdecoxib (1 mg/Kg) via gastric lavage 90 min after reperfusion and were sacrificed at 24h. * P < .05; ** P < 0.01. n = 8 per group. Ipsi: ipsilateral; contra: contralateral

Table 1
Relative cortical blood flow (percent of pre-ischemic) during and after middle cerebral occlusion in rat

	Cortical Blood Flow			
		Vehide	Valdecocixib	
pre-MCAO (T - 5 min)	ipsi contra	100 100	+/- +/-	1.5 1.7
MCAO (T + 10min)	ipsi contra	7.7 102	+/- +/-	0.3 2.4
Reperfusion (T + 5 min)	ipsi contra	110 102	+/- +/-	3.7 2.3
Reperfusion (T + 4h)	ipsi contra	184 99	+/- +/-	6.3 1.9
				155*
				103

Data are expressed as means ± S.E.
* P < .05; n = 8 per group, Ipsi: ipsilateral; contra: contralateral

Table 2

Physiological parameters mean arterial blood pressure and core body temperature during and after middle cerebral occlusion in rat

A Arterial Blood Gas				
	pH	pCO ₂ (mm Hg)	pO ₂ (mm Hg)	ABE (mEq/L)
pre - MCAO vehicle	7.38 +/- 0.01	35.9 +/- 2.0	213.3 +/- 13.2	-1.8 +/- 0.6
(T - 5 min) Valdecobix	7.36 +/- 0.01	36.0 +/- 2.8	217.5 +/- 15.1	-3.4 +/- 1.0

B Blood Pressure (mm Hg)			C Temperature (°C)		
	Vehicle	Valdecobix		Vehicle	Valdecobix
pre - MCAO (T - 5min)	86.7 +/- 2.2	87.1 +/- 2.3		34.4 +/- 0.1	34.2 +/- 0.2
MCAO (T + 10 min)	97.1 +/- 3.6	99.3 +/- 4.7		34.5 +/- 0.1	34.7 +/- 0.3

Arterial blood gases (A), mean arterial blood pressure (B) and body temperature (°C) (C) were measured before MCAO, 10 min post MCAO, immediately after reperfusion. Data are expressed as means ± S.E. n = 8 per group.