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Fenofibrate, a peroxisome proliferator-activated receptor α agonist, exerts neuroprotective effects in traumatic brain injury

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Abstract

Peroxisome proliferator-activated receptor α (PPARα) has been demonstrated to reduce inflammation in various inflammatory diseases. As traumatic brain injury (TBI) caused a neuroinflammatory response, we examined the effect of fenofibrate, a PPARα agonist, on the post-traumatic consequences caused by lateral fluid percussion of brain in rats. The effects of fenofibrate (50 and 100 mg/kg) were evaluated on the consequences of TBI in the early phase (6 and 24 h) and the late phase (7 days) after TBI. Neurological deficit, brain lesion, cerebral oedema and ICAM-1 expression were evaluated. Treatment with fenofibrate (given p.o. at 1 and 6 h after TBI) decreases the neurological deficit induced by TBI at 24 h. Furthermore, fenofibrate reduces brain oedema and ICAM-1 expression at 24 h post-TBI. Rats given fenofibrate at 1, 6, 24, 48 and 72 h after TBI show neurological recovery associated with a reduction of the brain lesion at 7 days post-TBI. The present data represents the first demonstration that fenofibrate, a PPARα agonist, exerts neuroprotective effects in TBI. The activation of receptor PPARα could be beneficial by counteracting the deleterious inflammatory response following TBI. This suggests that PPARα activation could be a new and promising therapeutic strategy for the treatment of brain trauma.
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Keywords: Cerebral oedema; Fenofibrate; Inflammation; Neuroprotection; Peroxisome proliferator-activated receptor α; Traumatic brain injury

Traumatic brain injury (TBI) remains one of the leading causes of death and disability in industrialized countries [3]. Despite numerous studies on animal models of TBI searching for therapeutic strategies, no neuroprotective therapy is currently available.

Peroxisome proliferator-activated receptor α (PPARα) is one of the three subtypes of the nuclear receptor PPAR family [15]. PPARs are implicated in several physiological processes, such as the regulation of lipoprotein, lipid metabolism and glucose homeostasis. Recent observations indicate that PPARα activators could reduce the inflammation induced in different inflammatory pathologies including asthma [31], hypertensive heart disease [9,20], hepatic inflammation [12] and cerebral ischemia [7]. As TBI induces also a deleterious neuroinflammatory response, it might be hypothesized that PPARα activation would be beneficial by counteracting this post-traumatic neuroinflammation. In order to investigate the role of PPARα activation on the consequences of brain trauma, we studied the effect of fenofibrate, a known PPARα activator, on the neurological deficit in the early (6 and 24 h) and the late phase (7 days) after TBI, on the cerebral oedema and the brain lesion caused by TBI. Additionally, we examined its effect on the expression of the inducible adhesion molecule, InterCellular Adhesion Molecule-1 (ICAM-1), used as a marker of post-traumatic inflammatory event.

Animals and materials: Animal care complied with the French regulations covering the protection of animals used for experimental and other scientific purposes (D2001-486), with the European Community regulations (Official Journal of European Community L358 12/18/1986),

Abbreviations: BWC, brain water content; COX2, cycloxygenase type 2; ICAM-1, intercellular adhesion molecule-1; IL-1, interleukin-1; NOS2, nitric oxide synthase type 2; PBS, phosphate-buffered saline; PPARα, peroxisome proliferator-activated receptor α; TBI, traumatic brain injury; TNFα, tumour necrosis factor alpha

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and it conformed to the *Guide for the Care and Use of Laboratory Animals* published by U.S. National Institutes of Health (NIH Publication no. 85–23, revised 1996). Male Sprague–Dawley rats were supplied by Iffa-Credo (L'Arbresle, France). Fenofibrate, methylcellulose, hydrogen peroxide, normal goat serum, diaminobenzidine, gelatin and sucrose were purchased from Sigma Chemicals Corporation (Saint Quentin-Fallavier, France). Mouse antibody raised against rat CD54, clone 1A29 (MCA773) was from Serotec (Cergy St Christophe, France) and biotinylated goat anti-mouse rat adsorbed antibody (AP-181B) from Chemicon (Euromedex, Mundolsheim, France). Streptavidin–biotin peroxidase complex (Vectastain Elite ABC) was obtained from Dako (Trappes, France).

Fluid percussion-induced brain injury: Male Sprague–Dawley rats (weighing 300–350 g) were anaesthetised with chloral hydrate (400 mg/kg, i.p.) and placed on a stereotaxic frame. During surgery, animals were positioned on a heating blanket (Harvard, UK) to maintain body normothermia ($37.5 \pm 0.5\,^{\circ}C$). Traumatic brain injury of moderate severity was induced by fluid percussion using the protocol previously described [2]. The scalp was incised and a 3 mm craniotomy was made lateral to the right temporoparietal cortex (coordinates: 3.5 mm anterior and 6 mm above the interaural line [21]) with a dental drill taking care to leave the dura mater intact. A 3 mm diameter polyethylene tube was placed over the dura mater, fixed securely into the craniotomy site with dental cement (Perfex, USA) and connected to a solenoid valve (Danfoss, Denmark). The opposite end of the valve was connected to a high performance liquid chromatography pump (Gilson). The system was filled with sterile water, providing a calibrated outflow pressure of 1.6–1.8 bar. A solenoid valve opening for 20 ms and controlled with a timer (Omron, Japan), triggered the percussion directly onto the dura mater. The applied cortical pressure was measured extracranially by a pressure transducer (Emka Technologies, France) connected to an oscilloscope (DSO 400, Gould, France). Immediately after fluid percussion, the tube was removed, the scalp sutured, and the animal was returned to its home cage warmed at 26–28 °C to recover from the anaesthesia. Thereafter, rats were group-housed under temperature- and light-controlled conditions with food and water ad libitum. Sham-operated rats underwent the same surgery except for percussion.

Neurological function: A neurological examination was performed in a blinded fashion using a grading scale (Table 1) [28]. Contralateral sensorimotor functions were examined by assessing placing reactions (leg hanging and visual), grasping reflex, righting reflex ("head tilted") in rats placed on a table. Rats were also examined for abnormal postures (forelimb flexion and thorax twisting). The scores for each item were summed and used as a global neurological score; the maximum was 9 for non-operated rats.

Brain lesion: Rats were anaesthetised with pentobarbital and killed by decapitation. Their brains were promptly removed, frozen in isopentane and stored at −40 °C. Serial coronal sections (50 μm thick) were cut in a cryostat (−15 °C) at 1 mm intervals, beginning at the level 13.7 to 1.7 mm relative to the interaural line [21]. The sections were stained with cresyl violet. The lesion areas were measured with an image analyzer (IMSTAR, France).

Table 1
Neurological examination grading scale

Item		Normal score	Deficit
Placing reactions			
Leg hanging	Left forepaw	1	0
	Left hindpaw	1	0
Visual		1	0
Grasping reflex	Left forepaw	1	0
	Left hindpaw	1	0
Righting reflex			
Head tilted	Left side	1	0
	Right side	1	0
Abnormal postures		Absent	Present
Thorax twisting		1	0
Left forelimb flexion		1	0
Global neurological score		9	

Brain oedema: Cerebral oedema was determined by measuring brain water content (BWC) using the wet weight–dry weight technique [1], and the results are expressed as a percentage of the water content. Rats were killed by an overdose of sodium pentobarbital (200 mg/kg, i.p.). The brains were promptly removed and a thick (4 mm) coronal slice was taken at the temporoparietal level. The slice was removed from the ipsilateral hemisphere. The fresh tissue samples were immediately weighed (wet weight) and placed in an incubator at 100 °C for 24 h. The samples were weighed once again to determine the dry weight. The BWC was calculated as follows:

$$\mathrm{BWC} = \left(\frac{(\text{wet weight} - \text{dry weight})}{\text{wet weight}} \right) \times 100$$

Preparation of brain tissue for immunohistochemistry: Rats were anaesthetised with sodium pentobarbital and perfused transcardially with 200 ml of heparinized saline followed by 400 ml of phosphate-buffered saline (PBS, 0.1 M, pH 7.4) containing 4% paraformaldehyde. The brains were then removed, kept for 1 h in the same fixative solution, and placed in two successive 10% sucrose solutions, each for 24 h. The brains were rapidly frozen in isopentane and stored at −40 °C until used. Serial coronal sections were cut (20 μm) on a cryostat (−18 °C, Jung CM 3000, Leica), collected on gelatine-coated slides, and processed for immunohistochemistry.

Immunohistochemistry of ICAM-1: All sections were incubated for 10 min in 0.3% hydrogen peroxide–10% ethanol in PBS before the primary antibody was added in order to quench the endogenous peroxidase activity. Non-specific binding sites were blocked using 2% normal goat serum in PBS for 30 min. Sections were then incubated overnight at 4 °C with the primary antibody (Mouse antibody against

ICAM-1 (CD54), diluted 1:200). Specific labelling was detected by incubating the sections for 60 min with the secondary antibody (biotinylated goat anti-mouse rat adsorbed antibody, 1:500 dilution). Reactions were amplified with streptavidin–biotin peroxidase complex. Diaminobenzidine was used as chromogen. Sections were dehydrated, and mounted. Photomicrographs were taken. As negative controls, alternative sections were incubated without the primary antibody. All immunohistochemical samples were examined by an investigator in a blinded fashion.

Experimental protocol: The doses chosen were previously used by others [24,25]. Rats were given fenofibrate (50 and 100 mg/kg) or its vehicle (water containing 0.2% methylcellulose), p.o. 1 h after TBI. The first neurological assessment was performed 6 h after brain injury. Immediately after, the rats were then given a second administration of fenofibrate or its vehicle. The second neurological assessment was done 24 h after TBI. The rats were then killed and the brain oedema determined. The same schedule of treatment was used to determine the effect of fenofibrate on immunohistochemistry of ICAM-1 at 24 h post-injury. For the evaluation of the effect of fenofibrate on brain lesion, rats were given fenofibrate (50 and 100 mg/kg) or its vehicle, p.o. 1 and 6 h post-TBI, followed by additional treatments 24, 48 and 72 h after TBI. At 7 days, the neurological assessment was done and the brain lesion determined.

Statistical analysis: Results are presented as mean ± S.E.M. Differences in neurological score were determined by non-parametric Kruskal–Wallis analysis, followed by a Mann–Whitney *U*-test. Differences in brain oedema were evaluated by one-way ANOVA with subsequent group comparisons by PLSD Fisher's test. Differences in brain lesion were evaluated by two-way ANOVA with subsequent group comparisons by PLSD Fisher's test. A P value of 0.05 was considered to be the threshold for a significant difference.

Neuroprotective effects of fenofibrate in the early and the late phase after TBI: Non-operated rats had a global neurological score of 9 ($n = 8$). Traumatic brain injury led to a significant decrease in the neurological score 6 h post-injury (6.0 ± 0.5 versus 8.6 ± 0.4 for sham-operated rats, $n = 8$, $P < 0.01$) that remained low 24 h post-injury (5.1 ± 0.7 versus 8.9 ± 0.1 for sham-operated rats, $P < 0.001$) (Fig. 1a and b). At 6 h post-TBI, fenofibrate at both doses did not modify the neurological score. At 24 h post-injury, rats given 50 mg/kg fenofibrate showed an improvement of the neurological score without reaching the statistical significance (7.1 ± 0.7, $n = 7$, $P = 0.09$), and those given 100 mg/kg fenofibrate demonstrated a significant increase of the score (7.6 ± 0.5, $n = 8$, $P < 0.05$). The neurological deficit induced by TBI remained significant at 7 days post-injury (9.0 ± 0.0 versus 6.1 ± 0.4 for vehicle-treated rats, $n = 8$, $P < 0.001$) (Fig. 2). Rats given fenofibrate at both doses showed improved neurological score (7.8 ± 0.4, $n = 5$, $P < 0.05$ for those given 50 mg/kg; 7.7 ± 0.5, $n = 6$, $P < 0.05$ for those given 100 mg/kg).

TBI induced a lesion located from the level 13.7 to 1.7 mm from interaural line (Fig. 3). Treatment with 50 mg/kg fenofibrate reduced the cerebral lesion ($P < 0.05$ versus vehicle-treated rats), whereas the high dose of fenofibrate wasn't devoid of any effect.

Anti-oedematous effect of fenofibrate: The BWC of non-operated and sham-operated rats were not different ($79.6 \pm 0.1\%$ versus $80.6 \pm 0.2\%$). TBI led to an increase of the BWC 24 h after injury ($84.9 \pm 0.5\%$ versus $80.6 \pm 0.2\%$, $P < 0.001$), which is reduced by the two doses of fenofibrate ($82.7 \pm 0.8\%$, $n = 7$, $P < 0.05$, for those given 50 mg/kg and $83.3 \pm 0.9\%$, $n = 8$, $P < 0.05$, for those given 100 mg/kg) (Fig. 4).

Effect of fenofibrate on ICAM-1 expression: TBI resulted in considerable immunostaining for ICAM-1 in the ipsilateral cortex (Fig. 5). Treatment of fenofibrate markedly reduced the expression of ICAM-1. No staining was detected in sections from non-operated rats (Fig. 5), in sections from injured rats when the primary antibody was omitted and in sections from sham-operated rats (not shown).

The present data represents the first demonstration that fenofibrate, a PPARα agonist, reduces the neurological

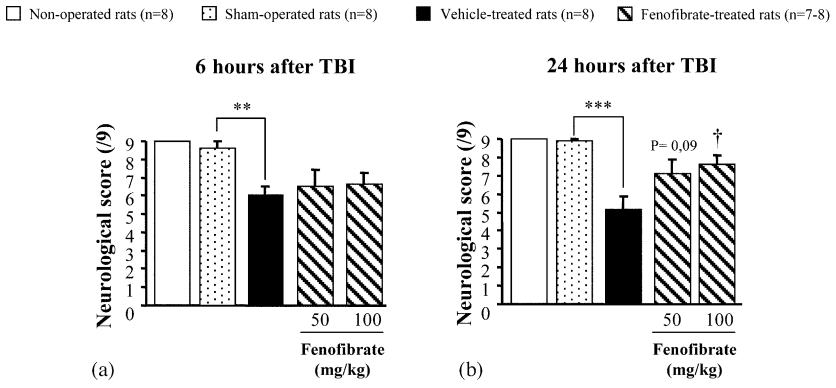

Fig. 1. Effect of fenofibrate on the neurological deficit in the early phase, 6 and 24 h, after TBI. Fenofibrate (50 and 100 mg/kg) or its vehicle (water containing 0.2% methylcellulose), were administrated p.o. 1 and 6 h after TBI. Neurological score was evaluated 6 h (a) and 24 h (b) after brain injury in non-operated rats ($n = 8$), sham-operated rats ($n = 8$), vehicle-treated rats ($n = 8$) and fenofibrate-treated rats ($n = 7$–8). $^{**}P < 0.01$ and $^{***}P < 0.001$ vs. sham-operated rats; $^{\dagger}P < 0.05$ vs. vehicle-treated rats.

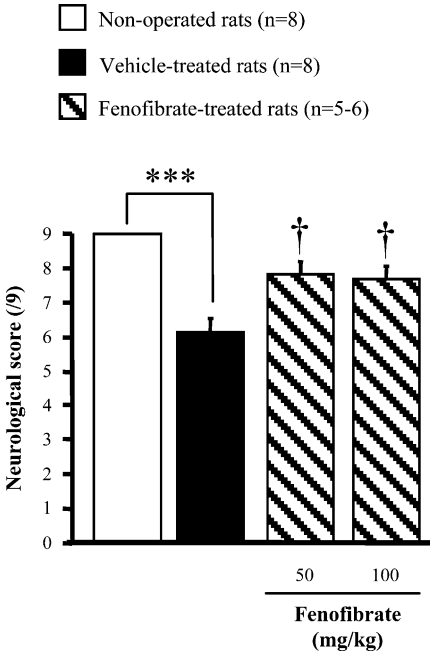

Fig. 2. Effect of fenofibrate on the neurological deficit in the late phase, 7 days, after TBI. Fenofibrate (50 and 100 mg/kg) or its vehicle (water containing 0.2% methylcellulose), were administrated p.o. 1 and 6 h post-TBI, followed by additional treatments 24, 48 and 72 h after TBI. The neurological assessment was evaluated 7 days after brain injury in non-operated rats ($n = 8$), vehicle-treated rats ($n = 8$) and fenofibrate-treated rats ($n = 5$–6). $^{***}P < 0.001$ vs. non-operated rats; $^{\dagger}P < 0.05$ vs. vehicle-treated rats.

deficit, the cerebral oedema and brain lesion caused by TBI. This is associated with decreased ICAM-1 expression induced by TBI.

In this study we report that treatment with fenofibrate, a known PPARα agonist [6,22], improved the neurological

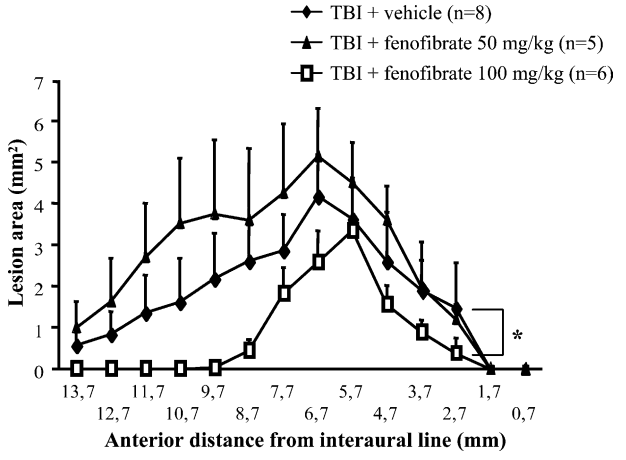

Fig. 3. Effect of fenofibrate on the brain lesion 7 days after TBI. Fenofibrate (50 and 100 mg/kg) or its vehicle (water containing 0.2% methylcellulose), were administrated p.o. 1 and 6 h post-TBI, followed by additional treatments 24, 48 and 72 h after TBI. The brain lesion was evaluated 7 days after brain injury in vehicle-treated rats ($n = 8$) and fenofibrate-treated rats ($n = 5$–6). The figure represents the rostrocaudal distribution of cerebral lesion areas plotted as a function of the anterior distance from interaural line. $^{*}P < 0.05$ vs. TBI + vehicle.

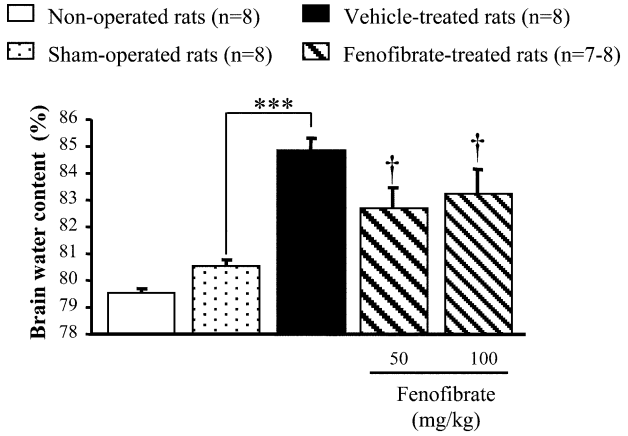

Fig. 4. Effect of fenofibrate on the cerebral oedema 24 h after TBI. Fenofibrate (50 and 100 mg/kg) or its vehicle (water containing 0.2% methylcellulose), were administrated p.o. 1 and 6 h after TBI. The cerebral oedema was evaluated 24 h after brain injury in non-operated rats ($n = 8$), sham-operated rats ($n = 8$), vehicle-treated rats ($n = 8$) and fenofibrate-treated rats ($n = 7$–8). $^{***}P < 0.001$ vs. sham-operated rats; $^{\dagger}P < 0.05$ vs. vehicle-treated rats.

deficit at 24 h and in the late phase, i.e. 7 days, after TBI. The neurological score is a clinically relevant endpoint, which is of particular importance since it is used in clinical trials of neuroprotective agents for TBI. In addition, the neurological recovery-promoting effect observed at 7 days with fenofibrate at 50 mg/kg was associated with a reduction of brain lesion. Recently, it has been demonstrated that the absence of functional PPARα gene significantly worsened the motor recovery score in spinal cord injury demonstrating that activation of PPARα by endogenous ligands have beneficial effects on tissue injury events associated with spinal cord trauma [11]. These results are also in accordance with other studies demonstrating beneficial effects of PPARα activation in acute ischemic stroke, which shares many pathophysiological pathways with TBI. Indeed treatment with fenofibrate reduces cerebral infarct size caused by cerebral ischemia [7,13]. However, in our study, even if 100 mg/kg fenofibrate exerted neurological recovery-promoting effect, this dosage didn't reduce the brain lesion, suggesting that a high dose associated with a long-term treatment with fenofibrate may induce adverse effects on cell death. Indeed some fibrates, in particular fenofibrate, have been shown to inhibit complex I of the respiratory chain, suggesting a role of fenofibrate in mitochondrial dysfunction [4]. Another hypothesis is that high dose of fenofibrate may exert massive anti-inflammatory effect by inhibiting cytokines (Tumour Necrosis Factor α, Interleukin-1) production. It is known that blockade of cytokines in the early phase is beneficial [27] but their presence is also fundamental for the processes of tissue repair and regeneration [18]. Thus, high dose of fenofibrate could counteract these beneficial effects.

The decrease in the neurological deficit at 24 h post-TBI was associated with a reduction in cerebral oedema. This data argues in favour of an anti-inflammatory effect of fenofibrate. To our knowledge, this anti-oedematous effect is the first to

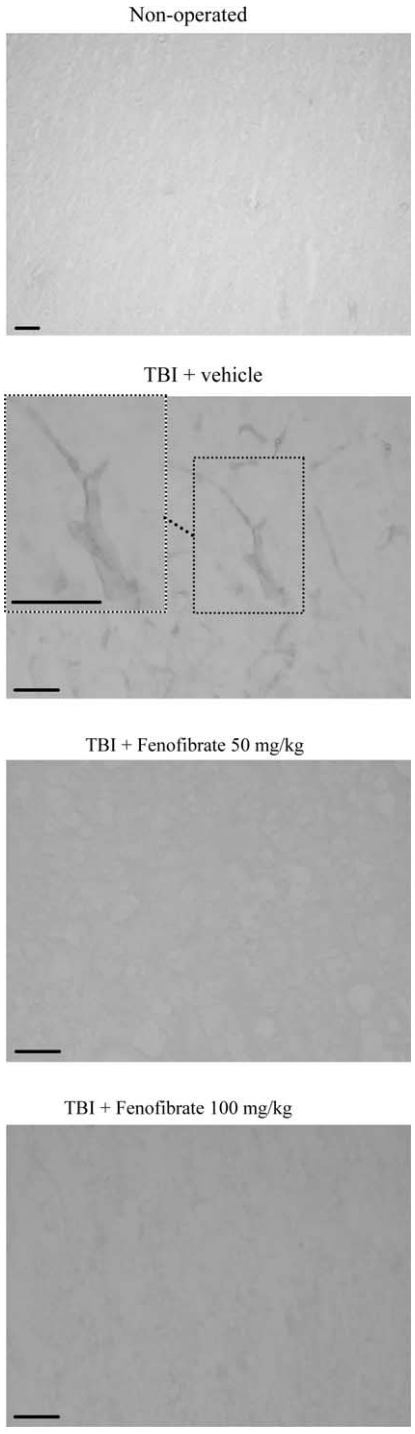

Fig. 5. Effect of fenofibrate on ICAM-1 24 h after TBI. Fenofibrate (50 and 100 mg/kg) or its vehicle (water containing 0.2% methylcellulose), were administrated p.o. 1 and 6 h after TBI. Staining was evaluated 24 h after brain injury in non-operated rats ($n = 4$), vehicle-treated rats ($n = 4$) and fenofibrate-treated rats ($n = 4$). Scale bar represents 100 μm.

be reported with a PPARα agonist in brain injury. To date, several studies have confirmed the anti-inflammatory properties of PPARα in vitro and in vivo. Indeed, mice deficient in PPARα exhibit a prolonged response to inflammatory stimuli [6,8]. In addition, by antagonizing the nuclear factor-kappa B signalling pathway, PPARα activators have been shown to decrease several inflammatory components, including adhesion molecules [9,17,20], cytokines (TNFα, IL-1β and -6) [12,20], COX2 [20,26] and NOS2 [26]. Since the neuroinflammatory response following TBI is characterised by several components including parenchyma infiltration by polymorphonuclear neutrophils [23], production of cytokines [19] and induction of NOS2 and COX2 [14,16], it could be hypothesized that these neurological recovery-promoting and anti-oedematous effects are mediated by the pleiotropic anti-inflammatory effects of fenofibrate. In this respect, we investigated the effect of fenofibrate on the induction of ICAM-1, an adhesion molecule involved in the polymorphonuclear neutrophil parenchyma infiltration after TBI. We showed that fenofibrate reduced ICAM-1 expression induced by TBI. This data is consistent with an anti-inflammatory mechanism of drug action. Our results are in agreement with other studies demonstrating that activation of PPARα results in the regulation of expression of adhesion molecule ICAM-1 in cardiac hypertrophy [9], splanchnic artery occlusion shock [5], myocardial [29] and cerebral [7] ischemia. Then the neurological recovery-promoting and anti-oedematous effect could be mediated partly by the decrease of ICAM-1 expression. However, previous data demonstrated that deficiency of ICAM-1 gene is associated with a reduction in post-traumatic brain oedema without affecting neurological deficit [30]. Then, at 24 h post-injury, the neurological recovery-promoting effects could be mediated by other anti-inflammatory mechanisms of fenofibrate, which need to be elucidated.

In conclusion, this study is the first one to demonstrate the beneficial effects of fenofibrate, a PPARα agonist, in TBI. Fenofibrate causes a substantial reduction in neurological deficit, cerebral oedema, lesion and ICAM-1 expression following TBI. Because fibrates have been previously reported to exert their pleiotropic pharmacological effects by activating PPARα [10], we hypothesized the neuroprotective effect of fenofibrate is PPARα-dependent. In this respect, Inoue et al. [13] have shown that fenofibrate requires PPARα expression to exert brain protection against cerebral ischemia. However, further studies are necessary to define more precisely the mechanisms underlying the beneficial effects we observed. These results should also be confirmed using other PPARα agonists. Our findings suggest that activation of PPARα could be a new promising therapeutic target for the clinical treatment of acute brain trauma.

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