4th Global Experts Meeting on
Neuropharmacology
September 14-16, 2016 San Antonio, Texas, USA

Gemfibrozil pretreatment affecting antioxidant defense system and inflammatory, but not Nrf-2 signaling pathways resulted in female neuroprotection and male neurotoxicity in the rat models of global cerebral ischemia-reperfusion

Leila Khalaj

Medical School, Alborz University of Medical Sciences, Karaj, Iran. Email: lkhalaj@yahoo.com

Introduction

Two important pathophysiological mechanisms involved in cerebral ischemia are oxidative stress and inflammation. During pathological conditions such as brain ischemia, the ability of free radicals production is believed to be greater than their elimination by endogenous antioxidant systems, so brain is highly injured due to the oxidative and neuroinflammatory processes (1,2). Fibrates as peroxisome proliferator-activated receptor (PPAR)-α ligands, are reported to have antioxidant and anti-inflammatory actions (3).

Aim

In this study, gemfibrozil, a fibrate is investigated for its therapeutic potential against global cerebral ischemia-reperfusion (I/R) injury of male and female rats.

Methods

This study particularly has focused on inflammatory and antioxidant signaling pathways, such as nuclear factor erythroid-related factor (Nrf)-2, as well as the activity of some endogenous antioxidant agents such as superoxide dismutase (SOD), catalase and glutathione level. besides, some inflammatory factors had been measured by Western blotting.

Table 1
MDA and GSH levels and antioxidant enzyme activities (SOD and CAT) in the hippocampus tissue of each study group

Group	MDA (nmol/mg protein)	SOD (U/mg protein)	CAT (µmol/min/mg protein)	GSH (µmol/g protein)
SM	1.781 ± 0.06	5.184 ± 0.31	1.821 ± 0.14	1.23 ± 0.05
IM	2.049 ± 0.15	3.878 ± 0.1*	2.497 ± 0.11	1.048 ± 0.05
TM	2.912 ± 0.17	2.67 ± 0.36**	2.534 ± 0.17	1.251 ± 0.03
SF	1.724 ± 0.19	4.883 ± 0.24	1.413 ± 0.081	0.967 ± 0.06
IF	3.063 ± 0.14¥	2.545 ± 0.13¥	0.536 ± 0.083¥	0.458 ± 0.03¥
TF	1.625 ± 0.13#	4.411 ± 0.25#	2.14 ± 0.16##	1.238 ± 0.02##

* $P < 0.05$ and ** $P < 0.01$; compared with male sham group

¥ $P < 0.05$; compared with female sham group

# $P < 0.05$ and ## $P < 0.01$; compared with female ischemic group

Results

It was found that pretreatment of animals with gemfibrozil prior to I/R resulted in a sexually dimorphic outcome (figure.1). Within females it proved to be protective, modulating inflammatory factors and inducing antioxidant defense system including SOD, catalase, as well as glutathione level (Table.1). However, Nrf-2 signaling pathway was not affected. It also decreased malondialdehyde level as an index of lipid peroxidation. In contrast, gemfibrozil pretreatment was toxic to males, enhancing the expression of inflammatory factors such as tumor necrosis factor-α, nuclear factor-κB, and cyclooxygenase-2, and decreasing Nrf-2 expression and SOD activity, leading to hippocampal neurodegeneration Figure 2, 3 and 4.

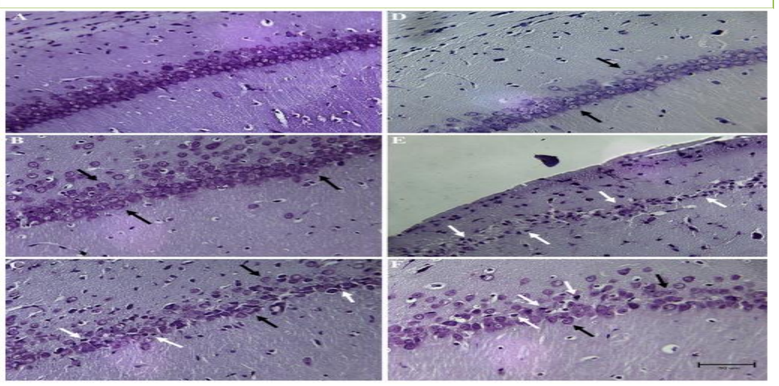

Fig. 1. Representative hippocampus sections stained with cresyl violet. × 400.

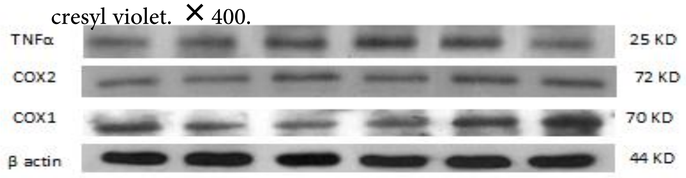

Fig. 2. Western blotting for TNFα, COX2 and COX1. SM:Sham male,IM:Ischemic male,TM:Treated male,SF:Sham female,IF:Ischemic female,TF:Treated female.

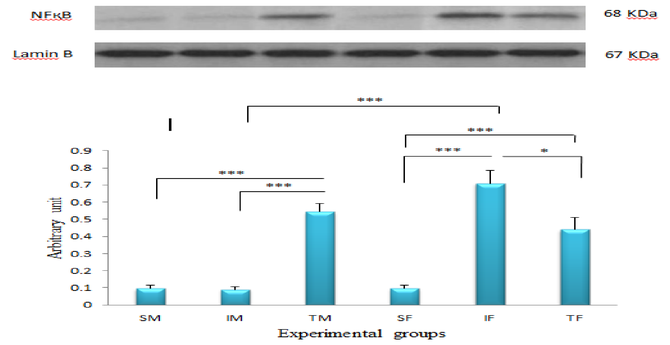

Fig. 3. Western blotting for NFKB.

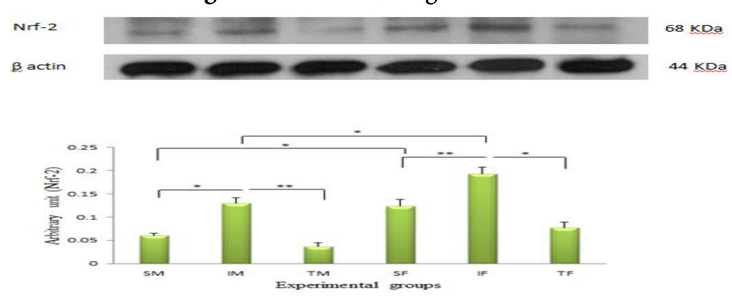

Fig. 4. Western blotting for Nrf-2, HO-1 and NQO1.

Conclusions

Considering that gemfibrozil is a commonly used anti-hyperlipidemic agent in clinic, undoubtedly more investigations are crucial to exactly unravel its sex-dependent neuroprotective/neurodegenerative potential.

Acknowledgments

This study was supported by Shahid beheshty University of Medical Sciences.

References

1. Candelario-Jalil E, Fiebich BL (2008) Cyclooxygenase inhibition in ischemic brain injury. Curr Pharm Des 14(14):1401–1418
2. Li M, Zhang X, Cui L, Yang R, Wang L, Liu L, Du W (2011) The neuroprotection of oxymatrine in cerebral ischemia/reperfusion is related to nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant response: role of Nrf2 and hemeoxygenase-1 expression. Biol Pharm Bull 34(5):595–601
3. Borges NC, Mendes GD, Barrientos-Astigarraga RE, Zappi E, Mendes FD, De Nucci G (2005) Comparative bioavailability study with two gemfibrozil tablet formulations in healthy volunteers. Arzneimittelforschung 55:382–386.