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Gemfibrozil pretreatment resulted in a sexually dimorphic outcome in the rat models of global cerebral ischemia-reperfusion via modulation of mitochondrial pro-survival and apoptotic cell death factors as well as MAPKs.

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Introduction

Inducers of mitochondrial biogenesis are widely under investigation for use in a novel therapeutic approach in neurodegenerative disorders. The ability of Gemfibrozil, a fibrate, is investigated for the first time to modulate mitochondrial pro-survival factors involved in the mitochondrial biogenesis signaling pathway, including peroxisome proliferator-activated receptor coactivator-1α (PGC-1α), nuclear respiratory factor (NRF-1), and mitochondrial transcription factor A (TFAM) in the brain. Gemfibozil is clinically administered to control hyperlipidemia. It secondarily prevents cardiovascular events such as cardiac arrest in susceptible patients (1, 2).

Aim

In this study, pretreatment of animals with gemfibrozil prior to ischemia-reperfusion (I/R) resulted in a sexually dimorphic outcome.

Methods

The current study evaluated the role of gemfibrozil pretreatment against 4-vessel occlusion cerebral ischemia through measuemnet of apoptosi, mitochondrial biogenesis and MAPK peroteins in the hippocampus.

Fig.1. Representative hippocampi sections stained with TUNEL. **a**, **d**, **b** show hippocampal CA1 field of male and female sham groups, and male ischemic group, respectively. Male ischemic group stained negative for TUNEL-positive neurons (**b**). Neurons were moderately TUNEL-stained in gemfibrozil-pretreated male ischemic group (*arrows*) (**c**). The large number of TUNEL-positive neurons detected in female ischemic group (*arrows*) (**e**), were significantly decreased in their respective gemfibrozil-pretreated group (**f**). Magnification, ×400.

Results

While the expression of NRF-1 and TFAM were induced in gemfibrozil-pretreated met-estrous females, they were suppressed in males. Gemfibrozil also proved to be neuroprotective in met-estrous females, as it inhibited caspase-dependent apoptosis while in males it led to hippocampal neurodegeneration via activation of both the caspase-dependent and caspase-independent apoptosis (figures, 1, 2 and 3). In the mitogen-activated protein kinase (MAPKs) pathway (figure.4), gemfibrozil pretreatment induced the expression of extracellular signal-regulated kinases (ERK1/2) in met-estrous females and reduced it in males.

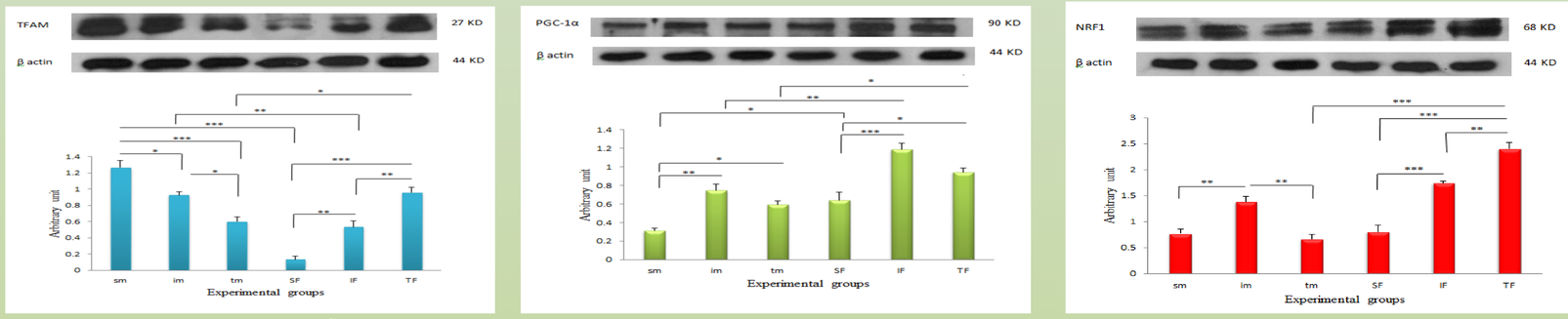


Fig. 2. Western blotting for TFAM, PGC-1$^{\alpha}$ and NRF-1. SM:Sham male,IM:Ischemic male,TM:Treated male,SF:Sham female,IF:Ischemic female,TF:Treated female.

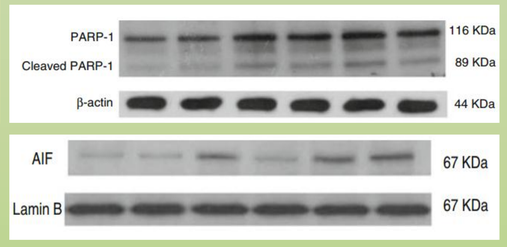
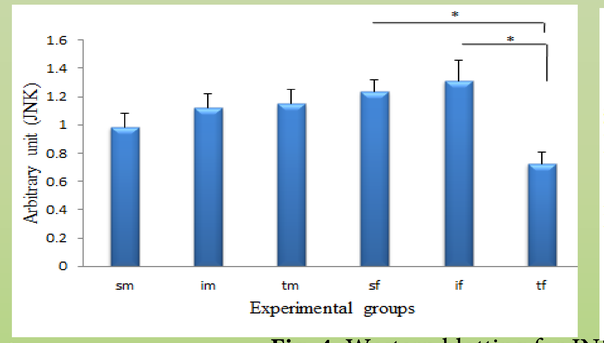


Fig. 3. Western blotting for PARP-1 and AIF.



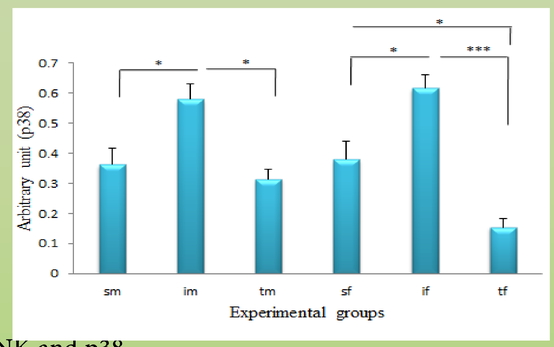


Fig. 4. Western blotting for JNK and p38.

Conclusions

These findings correlatively point to the sexual-dimorphic effects of gemfibrozil in global cerebral I/R context by affecting important factors involved in the mitochondrial biogenesis, MAPKs, and apoptotic cell death pathways.

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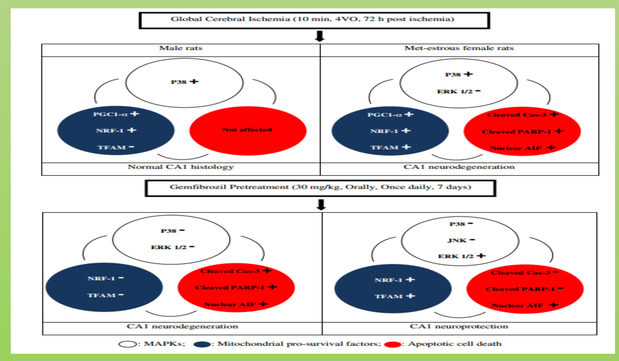

The graphical abstract represents major changes of the studied molecules affected by global cerebral ischemia–reperfusion and gemfibrozil pretreatment, resulting in the final outcome of male neurotoxicity, female neuroprotection in the CA1 region of hippocampus; *plus sign* induction; *minus sign* reduction

References

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