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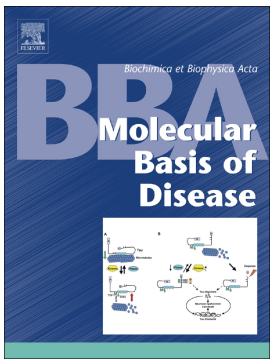

New therapeutic activity of metabolic enhancer Piracetam in treatment of neurodegenerative disease: Participation of caspase independent death factors, oxidative stress, inflammatory responses and apoptosis

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New therapeutic activity of metabolic enhancer Piracetam in treatment of neurodegenerative disease: participation of caspase independent death factors, oxidative stress, inflammatory responses and apoptosis

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Abstract

Piracetam, a nootropic drug that has been clinically used for decades but remains enigmatic due to no distinct understanding of its mechanism of action. The present study aimed to investigate the role of caspase independent pathway in piracetam mediated neuroprotection. LPS administration caused significant alterations in oxidative stress related parameters like glutathione, glutathione reductase and increased lipid peroxidation. LPS administration also caused augmented expression of inflammatory cytokines and astrocytes activation. Piracetam treatment offered significant protection against LPS induced oxidative and inflammatory parameters and inhibited astrocytes activation. LPS administration caused augmented level of reactive oxygen species and depleted mitochondrial membrane potential which were attenuated with piracetam treatment. This study for the first time demonstrates the role of caspase independent death factors in piracetam induced neuroprotective effects in rat brain. Translocation of mitochondrial resident apoptosis inducing factor and endonuclease G to nucleus through cytosol after LPS administration was significantly blocked with piracetam treatment. Further, LPS induced DNA fragmentation along with up regulated Poly [ADP-ribose] polymerase 1 (PARP1) levels were also inhibited with piracetam treatment. Apoptotic death was confirmed by the cleavage of caspase 3 as well as histological alteration in rat brain regions. LPS administration caused significantly increased level of cleaved caspase 3, altered neuronal morphology and decreased neuronal density which were restored with piracetam treatment. Collectively our findings indicate that piracetam offered protection against LPS induced inflammatory responses and cellular death including its antioxidative antiapoptotic activity with its attenuation against mitochondria mediated caspase independent pathway.

Key Words: Piracetam; Lipopolysaccharide; Oxidative stress; apoptosis inducing factor; endonuclease-G; poly (ADP-ribose) polymerase-1; DNA damage.

Introduction

Piracetam (2-oxo-1-pyrrolidine acetamide) is a cyclic derivative of the neurotransmitter γ-aminobutyric acid (GABA), belongs to group of racetams and also termed as "nootropic"