Activation of the Melanocortin-4 Receptor Prevents Oxidative Damage and Mitochondrial Dysfunction in Cultured Hippocampal Neurons Exposed to Ethanol

Quintanilla R.A.

Pérez M.J.

Aranguiz A.

Tapia-Monsalves C.

Mendez G.

Excessive alcohol intake affects hippocampal function and neuronal communication through oxidative stress and mitochondrial impairment. Previous studies have suggested that the melanocortin system (MCS) plays an essential role in alcohol consumption and addiction. The MCS is a hypothalamic region involved in regulating inflammatory processes in the brain, and its pharmacological activation through the melanocortin-4 receptor (MC4R) reduces both alcohol consumption and the neuroinflammatory responses in the brain. However, the cellular mechanisms involved in the beneficial actions of MCS against ethanol toxicity are not entirely understood. The objective of this study was to investigate the protective role of the MC4R pharmacological activator RO27-3225 on oxidative damage and mitochondrial impairment present in hippocampal neuronal cultures acutely exposed to ethanol (50, 75 mM, 24 h). Pre-treatment with RO27-3225 (250 nM, 1 h) prevented reactive oxygen species (ROS) increase, dysregulation of cytosolic calcium homeostasis, and mitochondrial potential loss induced by ethanol. Improvement of mitochondrial failure produced by RO27-3225 was accompanied by a significant increase in ATP production in ethanol-treated neurons. More importantly, RO27-3225 promoted the activation of the antioxidant pathway Nrf-2, demonstrated by an increase in the expression and nuclear translocation of Nrf-2, and upregulation of mRNA levels of NAD(P)H quinone oxidoreductase 1 (NQO1), an antioxidant enzyme which expression is activated by this pathway. These results suggest that the stimulation of MC4R prevents oxidative damage and mitochondrial stress induced by ethanol through the activation of the

Nrf-2 pathway in cultured hippocampal neurons. These results are novel and demonstrate the critical function of MC4R in promoting antioxidant defense and reducing mitochondrial damage produced by ethanol in the brain.

Alcohol

Binge drinking

Ethanol

Mitochondria

Nrf-2

Oxidative stress

adenosine triphosphate

alcohol

melanocortin 4 receptor

neuroprotective agent

reactive oxygen metabolite

reduced nicotinamide adenine dinucleotide dehydrogenase (ubiquinone)

ro 27 3225

transcription factor Nrf2

unclassified drug

adolescent

animal cell

animal tissue

antioxidant activity

Article

calcium homeostasis

cell stress

cell viability

controlled study

disorders of mitochondrial functions

embryo

enzyme activation

hippocampal neuronal culture

immunofluorescence

male

mitochondrial membrane potential

nonhuman

oxidative stress

priority journal

protein expression

protein function

protein localization

rat

real time polymerase chain reaction

signal transduction

upregulation