Mfn2 downregulation in excitotoxicity causes mitochondrial dysfunction and delayed neuronal death

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Mitochondrial fusion and fission is a dynamic process critical for the maintenance of mitochondrial function and cell viability. During excitotoxicity neuronal mitochondria are fragmented, but the

member of the mitochondrial fusion/fission machinery whose expression is reduced in in vitro and in

mechanism underlying this process is poorly understood. Here, we show that Mfn2 is the only

vivo models of excitotoxicity. Whereas in cortical primary cultures, Drp1 recruitment to mitochondria

plays a primordial role in mitochondrial fragmentation in an early phase that can be reversed once

the insult has ceased, Mfn2 downregulation intervenes in a delayed mitochondrial fragmentation

phase that progresses even when the insult has ceased. Downregulation of Mfn2 causes

mitochondrial dysfunction, altered calcium homeostasis, and enhanced Bax translocation to

mitochondria, resulting in delayed neuronal death. We found that transcription factor MEF2

regulates basal Mfn2 expression in neurons and that excitotoxicity-dependent degradation of MEF2

causes Mfn2 downregulation. Thus, Mfn2 reduction is a late event in excitotoxicity and its targeting

may help to reduce excitotoxic damage and increase the currently short therapeutic window in

stroke. Synopsis Excitotoxicity leads to mitochondrial fragmentation, altered calcium homeostasis and neuronal death in two phases: a reversible Drp1-dependent one, followed by the irreversible degradation of MEF2, causing reduced Mfn2 transcription and Bax translocation to mitochondria. MEF2 regulates Mfn2 basal transcription in neurons. MEF2 degradation in excitotoxicity causes Mfn2 downregulation. Reduced Mfn2 expression causes mitochondrial dysfunction and altered calcium homeostasis. Mfn2 downregulation in excitotoxicity participates in delayed cell death by facilitating Bax recruitment to mitochondria. Excitotoxicity leads to mitochondrial fragmentation, altered calcium homeostasis and neuronal death in two phases: a reversible Drp1-dependent one, followed by the irreversible degradation of MEF2, causing reduced Mfn2 transcription and Bax translocation to mitochondria. © 2014 The Authors.

excitotoxicity

mitochondrial dynamics

neuron

transcriptional regulation

calcium ion

mitofusin 2

myocyte enhancer factor 2

protein Bax

Bax protein, rat

calcium

Drp1 protein, rat

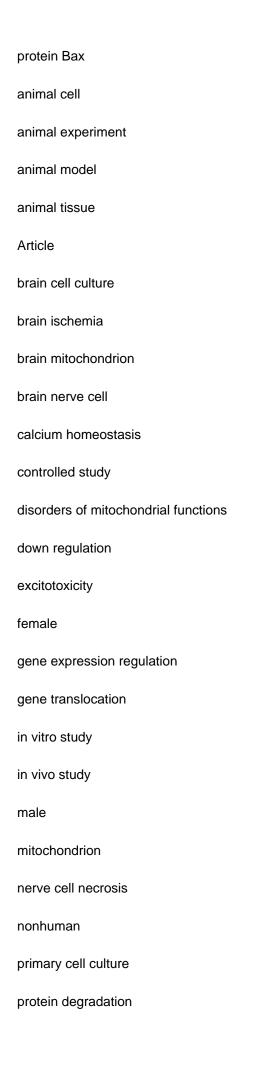
dynamin

membrane protein

mitochondrial protein

mitofusin 2 protein, rat

myocyte enhancer factor 2



protein expression
rat
transcription regulation
animal
cell culture
cell death
cell line
down regulation
gene expression regulation
genetics
homeostasis
human
metabolism
mitochondrial dynamics
mutation
nerve cell
physiology
Sprague Dawley rat
Animals
bcl-2-Associated X Protein
Calcium
Cell Death
Cell Line
Cells, Cultured
Down-Regulation
Dynamins

Gene Expression Regulation
Homeostasis
Humans
Male
MEF2 Transcription Factors
Membrane Proteins
Mitochondria
Mitochondrial Dynamics
Mitochondrial Proteins
Models, Animal
Mutation
Neurons
Rats
Rats, Sprague-Dawley