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 mechanism underlying this process is poorly understood. Here, we show that Mfn2 is the only member of the mitochondrial fusion/fission machinery whose expression is reduced in in vitro and in 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.

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 Bax

animal cell

animal experiment

animal model

animal tissue

Article

brain cell culture

brain ischemia

brain mitochondrion

brain nerve cell

calcium homeostasis

controlled study

disorders of mitochondrial functions

down regulation

excitotoxicity

female

gene expression regulation

gene translocation

in vitro study

in vivo study

male

mitochondrion

nerve cell necrosis

nonhuman

primary cell culture

protein degradation

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