Excitotoxicity as a target against neurodegenerative processes

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The global burden of neurodegenerative diseases is alarmingly increasing in parallel to the aging of population. Although the molecular mechanisms leading to neurodegeneration are not completely understood, excitotoxicity, defined as the injury and death of neurons due to excessive or prolonged exposure to excitatory amino acids, has been shown to play a pivotal role. The increased release and/or decreased uptake of glutamate results in dysregulation of neuronal calcium homeostasis, leading to oxidative stress, mitochondrial dysfunctions, disturbances in protein turn-over and neuroinflammation. Despite the anti-excitotoxic drug memantine has shown modest beneficial effects in some patients with dementia, to date, there is no effective treatment capable of halting or curing neurodegenerative diseases such as Alz-heimer?s disease, Parkinson disease, Huntington?s disease or amyotrophic lateral sclerosis. This has led to a grow-ing body of research focusing on understanding the mechanisms associated with the excitotoxic insult and on uncovering potential therapeutic strategies targeting these mechanisms. In the present review, we examine the molecular mechanisms related to excitotoxic cell death. Moreover, we provide a comprehensive and updated state of the art of preclinical and clinical investigations targeting excito-toxic-related mechanisms in order to provide an effective treatment against neurodegeneration.

Alzheimer?s disease

Calcium

ER stress

Glutamate

Neurodegeneration

Neuroinflammation

Oxidative stress

Parkinson?s disease

adenosine triphosphatase

amino acid

apoptosome

apoptotic protease activating factor 1

BH3 protein

calcium

calcium channel blocking agent

calpain

caspase 9

cinnarizine

DNA

flunarizine

glutamic acid

glyceraldehyde 3 phosphate dehydrogenase

inositol 1,4,5 trisphosphate receptor

ion channel

ionotropic receptor

isoflurane

lomerizine

memantine

n methyl dextro aspartic acid receptor

nimodipine

nitric oxide

propofol

reactive oxygen metabolite

reduced nicotinamide adenine dinucleotide phosphate oxidase

sodium calcium exchange protein

unindexed drug

verapamil

zonisamide

Alzheimer disease

amyotrophic lateral sclerosis

apoptosis

calcium homeostasis

cell death

cytotoxicity

degenerative disease

dementia

disease exacerbation

disorders of mitochondrial functions

DNA fragmentation

dopaminergic nerve cell

endoplasmic reticulum stress

excitotoxicity

frontotemporal dementia

human

Huntington chorea

in vitro study

in vivo study

inflammation

mitochondrial permeability

molecular mechanics

motor performance

nerve degeneration

nervous system inflammation

nitrosylation

oxidative stress

Parkinson disease

pathophysiology

priority journal

protein processing

Review

traumatic brain injury

unfolded protein response