Neuroprotection targeting protein misfolding on chronic cerebral hypoperfusion in the context of metabolic syndrome

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Metabolic syndrome (MetS) is a cluster of risk factors that lead to microvascular dysfunction and chronic cerebral hypoperfusion (CCH). Long-standing reduction in oxygen and energy supply leads to brain hypoxia and protein misfolding, thereby linking CCH to Alzheimer's disease. Protein misfolding results in neurodegeneration as revealed by studying different experimental models of CCH. Regulating proteostasis network through pathways like the unfolded protein response (UPR), the ubiquitin-proteasome system (UPS), chaperone-mediated autophagy (CMA), and macroautophagy emerges as a novel target for neuroprotection. Lipoxin A4 methyl ester, baclofen, URB597, N-stearoyl-L-tyrosine, and melatonin may pose potential neuroprotective agents for rebalancing the proteostasis network under CCH. Autophagy is one of the most studied pathways of proteostatic cell response against the decrease in blood supply to the brain though the role of the UPR-specific chaperones and the UPS system in CCH deserves further research. Pharmacotherapy targeting misfolded proteins at different stages in the proteostatic pathway might be promising in treating cognitive impairment following CCH.

Chaperones

Chronic cerebral hypoperfusion

Endoplasmic reticulum stress

Metabolic syndrome

Neurodegenerative diseases

Neuroprotection

Protein misfolding

activating transcription factor 6

amyloid beta protein

baclofen

cyclohexylcarbamic acid 3' carbamoylbiphenyl 3 yl ester

inositol requiring enzyme 1 alpha

lipoxin A4 methyl ester

melatonin

n stearoyl levo tyrosine

neuroprotective agent

palmidrol

proteasome

protein RNA like endoplasmic reticulum kinase

tau protein

ubiquitin

unclassified drug

X box binding protein 1

Alzheimer disease

APOE gene

atherosclerosis

autophagy

behavior disorder

bilateral common carotid artery occlusion

brain atrophy

brain blood flow

brain disease

brain perfusion

carotid artery obstruction

chaperone-mediated autophagy

chronic cerebral hypoperfusion

cognitive defect

disease association

endoplasmic reticulum stress

genetic risk

hippocampal atrophy

human

hyperglycemia

hypertension

hypertriglyceridemia

hypoxia

insulin resistance

lipid diet

macroautophagy

metabolic syndrome X

nerve degeneration

neuroprotection

non insulin dependent diabetes mellitus

nonhuman

obesity

oxidative stress

oxygen glucose deprivation

pathogenesis

protein deficiency

protein function

protein homeostasis

protein misfolding

protein misfolding disorder

protein phosphorylation

risk factor

Short Survey

signal transduction

unfolded protein response

vascular disease