# Restoration of aberrant mTOR signaling by intranasal rapamycin reduces oxidative damage: Focus on HNE-modified proteins in a mouse model of down syndrome

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Increasing evidences support the notion that the impairment of intracellular degradative machinery is responsible for the accumulation of oxidized/misfolded proteins that ultimately results in the deposition of protein aggregates. These events are key pathological aspects of ?protein misfolding diseases?, including Alzheimer disease (AD). Interestingly, Down syndrome (DS) neuropathology shares many features with AD, such as the deposition of both amyloid plaques and neurofibrillary tangles. Studies from our group and others demonstrated, in DS brain, the dysfunction of both proteasome and autophagy degradative systems, coupled with increased oxidative damage. Further, we observed the aberrant increase of mTOR signaling and of its down-stream pathways in both DS brain and in Ts65Dn mice. Based on these findings, we support the ability of intranasal rapamycin treatment (InRapa) to restore mTOR pathway but also to restrain oxidative stress resulting in the decreased accumulation of lipoxidized proteins. By proteomics approach, we were able to identify specific proteins that showed decreased levels of HNE-modification after InRapa treatment compared with vehicle group. Among MS-identified proteins, we found that reduced oxidation of arginase-1 (ARG-1) and protein phosphatase 2A (PP2A) might play a key role in reducing brain damage associated with synaptic transmission failure and tau hyperphosphorylation. InRapa treatment, by reducing ARG-1 protein-bound HNE levels, rescues its enzyme activity and conceivably contribute to the recovery of arginase-regulated functions. Further, it was shown that PP2A inhibition induces tau hyperphosphorylation and spatial memory deficits. Our data suggest that InRapa was able to rescue PP2A activity as suggested by reduced p-tau levels. In summary, considering that mTOR pathway is a central hub of multiple intracellular signaling, we propose that InRapa treatment is able to lower the lipoxidation-mediated damage to proteins, thus representing a valuable therapeutic strategy to reduce the early development of AD pathology in DS population. 

Down syndrome

mTOR

Oxidative stress

Protein-bound HNE

Rapamycin

4 hydroxynonenal

arginase

arginase 1

mammalian target of rapamycin

phosphoprotein phosphatase 2A

rapamycin

tau protein

biological marker

proteasome

rapamycin

target of rapamycin kinase

Alzheimer disease

amnesia

animal experiment

animal model

animal tissue

antioxidant activity

Article

brain protection

controlled study

dose response

Down syndrome

enzyme activity

enzyme inhibition

female

lipid peroxidation

male

mouse

mouse model

mTOR signaling

nonhuman

oxidation

oxidative stress

priority journal

protein analysis

protein phosphorylation

proteomics

spatial memory

synaptic transmission

treatment duration

animal

autophagy

disease model

drug effect

intranasal drug administration

metabolism

procedures

signal transduction

Administration, Intranasal

Animals

Autophagy

Biomarkers

Disease Models, Animal

Down Syndrome

Female

Male

Mice

Oxidative Stress

Proteasome Endopeptidase Complex

Proteomics

Signal Transduction

Sirolimus

TOR Serine-Threonine Kinases