Intranasal rapamycin ameliorates Alzheimer-like cognitive decline in a mouse model of Down syndrome

Tramutola A.

Lanzillotta C.

Barone E.

Arena A.

Zuliani I.

Mosca L.

Blarzino C.

Butterfield D.A.

Perluigi M.

Di Domenico F.

Background: Down syndrome (DS) individuals, by the age of 40s, are at increased risk to develop Alzheimer-like dementia, with deposition in brain of senile plaques and neurofibrillary tangles. Our laboratory recently demonstrated the disturbance of PI3K/AKT/mTOR axis in DS brain, prior and after the development of Alzheimer Disease (AD). The aberrant modulation of the mTOR signalling in DS and AD age-related cognitive decline affects crucial neuronal pathways, including insulin signaling and autophagy, involved in pathology onset and progression. Within this context, the therapeutic use of mTOR-inhibitors may prevent/attenuate the neurodegenerative phenomena. By our work we aimed to rescue mTOR signalling in DS mice by a novel rapamycin intranasal administration protocol (InRapa) that maximizes brain delivery and reduce systemic side effects. Methods: Ts65Dn mice were administered with InRapa for 12 weeks, starting at 6 months of age demonstrating, at the end of the treatment by radial arms maze and novel object recognition testing, rescued cognition. Results: The analysis of mTOR signalling, after InRapa, demonstrated in Ts65Dn mice hippocampus the inhibition of mTOR (reduced to physiological levels), which led, through the rescue of autophagy and insulin signalling, to reduced APP levels, APP processing and APP

metabolites production, as well as, to reduced tau hyperphosphorylation. In addition, a reduction of oxidative stress markers was also observed. Discussion: These findings demonstrate that chronic InRapa administration is able to exert a neuroprotective effect on Ts65Dn hippocampus by reducing AD pathological hallmarks and by restoring protein homeostasis, thus ultimately resulting in improved cognition. Results are discussed in term of a potential novel targeted therapeutic approach to reduce cognitive decline and AD-like neuropathology in DS individuals. © 2018 The Author(s).

Alzheimer disease

APP

Autophagy

Down syndrome

mTOR

Oxidative stress

Rapamycin

Tau

amyloid precursor protein

rapamycin

tau protein

Alzheimer disease

animal experiment

animal model

Article

autophagy

cognitive defect

controlled study

dose response

Down syndrome

drug effect

drug efficacy

female

hippocampus

insulin signaling

male

metabolite

mouse

mTOR signaling

neuroprotection

nonhuman

novel object recognition test

oxidative stress

priority journal

protein homeostasis

protein phosphorylation

radial arm maze test

single drug dose

treatment outcome