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بسم اللّه الرحمن الرحيم

مركز الشبكات وتكنولوجيا المعلومات

قسم التوثيق الإلكتروني

Mona Maghraby

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم باللّه العظيم أن المادة التي تم توثيقها وتسجيلها

علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

Department of Biochemistry

The effect of the flavonoid quercetin on the modulation of the amyloid pathway in Aluminum chloride-induced Alzheimer disease in rats

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disease clinically characterized by progressive cognitive impairment. Exposure to aluminum (Al), a potent neurotoxin, causes oxidative stress and initiates the development of Alzheimer's disease. Quercetin (Q), a bioflavonoid, has been reported to slow down AD progression. The aim of this study was to look into the role of Q in treating and protecting $AlCl_3$-induced AD rats by looking into the molecular processes that underpin its neuroprotective and therapeutic effects. In this study, male Wistar rats were subjected to a two independent experiments; experiment I (effect of post treatment with quercetin) in which the rats were distributed into; a normal control group which induced with saline for 56 days , two quercetin doses groups that is orally administrated with Q (25 and 50 mg/kg) for 28 days after induction with saline for 28 days, AD group, that is IP(Intraperitoneally) administrated with $AlCl_3$(50 mg/kg) for 28 days followed by saline for 28 days, and the treated groups :($AlCl_3$ followed by Q25), and ($AlCl_3$ followed by Q50) for 28 days, as well as, experiment II (Coadministration of $AlCl_3$ with quercetin) that divided into a normal control (NC) group, two quercetin doses (both 25 and 50 mg/ kg) groups, $AlCl_3$ (AD) group, co-administration with $AlCl_3$ + Q25 group, and co-administration with $AlCl_3$ + Q50 group for 56 consecutive days. Behavioral assessments were carried out on rats in the final week of both experiments. Hippocampi were collected for neurochemical and histological evaluations, as well as gene expression assessment. The results of experiment 1 demonstrated that administration of Q to an $AlCl_3$-induced AD rat model reduced behavioral impairments, improved cholinergic and dopaminergic dysfunctions, and decreased the formation of insoluble amyloid plaques in the hippocampus. In the hippocampus, these beneficial effects of Q were linked to downregulation of

APP, BACE1, APH1, and PSEN1 and upregulation of ADAM10 and ADAM17 gene expression levels. Moreover, experiment 2 resulted in; the co-administration of quercetin (50 mg/kg) has a substantial effect on learning and memory deficits by reducing eosinophilic plaques and β -amyloid plaque deposits, as well as restoring the activity of Acetylcholine esterase (AchE) and increasing dopamine (DA) level. Furthermore, it significantly decreased levels of amyloid precursor protein (APP), β-amyloid converting enzyme 1 (BACE1), and Presenilin I (PSEN1) and increased the expression of ADAM17 in the hippocampus tissue compared to $AlCl_3$ group. Conclusion: Q treatment might attenuate neurotransmission impairment, Aβ aggregation in the hippocampus, and behavioral deficits in the $AlCl_3$-induce AD rat model via up-regulating and stimulating the non-amyloidogenic pathway leading to the inhibition of the amyloidogenic pathway in the mild Alzheimer. In addition, co-administration of quercetin with the $AlCl_3$-induced AD rats could also inhibit the progression of cognitive impairment in the hippocampus tissue in the severe AD through inhibition of the genes of the amyloidogenic pathway.

Contents

List of Abbreviations

AD	Alzheimer's disease
AChE	Acetylcholine Esterase
ADAM	Membrane-bound disintegrin metalloproteinase
AICD	APP intracellular domain
$AlCl_3$	Aluminum chloride
Alum	Aluminum sulphate
Aph1	Anterior pharynx-defective 1
APOE	Apolipoprotein E
APP	Amyloid precursor protein
APP CTF83/αCTF	APP C-terminal fragment 83
APP βCTF /C99	membrane-associated C-terminal APP fragment
Aβ	Amyloid-Beta
BACE1	β-secretase 1
BBB	Blood Brain Barrier
BChE	Butyryl cholinesterase
CAA	Cerebral Amyloid Angiopathy
CDK5	Cyclin dependent kinase
COX-2	cyclo oxygenase 2
DA	Dopamine
DTNB	5,5'-dithio-bis-2-nitrobenzoic acid
EOAD	Early-Onset Alzheimer Disease
ep	eosinophilic plaques
GSK-3β	Glycogen synthase kinase 3 beta
H & E	Hematoxylin and eosin stain
HC	Habenular Commissure
HD	Huntington's disease
IL-6	Interleukin 6
iNOS	inducible nitric oxide synthase
IP	Intraperitoneally
IRE	Iron responsive element
LB	Lewy bodies

LBD	Lewy Body Dementia
LOAD	late-onset Alzheimer's disease
MAPKs	Mitogen Activated Protein Kinase
MCI	Mild cognitive impairment
MD	Mixed Dementia
Nct	Nicastrin
NF-kB	Nuclear factor kappa B
NFT	Neurofibrillary tangles
NMDA	N-methyl-d-aspartate
Nrf-2	Nuclear factor (erythroid-derived 2)-like 2
PD	Parkinson's disease
PDD	Parkinson's disease dementia
Pen-2	Presenilin enhancer 2
PI3K/Akt/GSK3β	phosphoinositide3 kinase/protein kinase B/Glycogen synthase kinase3β
pn	pyramidal neuron
PON2	paraoxonase 2
PP2A	protein phosphatase 2A
PSEN1	Presenilin 1
Q	Quercetin
ROS	Reactive Oxygen Species
SAP97	Synapse-associated protein 97
sAPP	soluble APP-fragment
SE	Standard error of mean
SOD	superoxide dismutase
SP	Senile plaques
TACE	Tumor necrosis factor-alpha converting enzyme
TBI	Traumatic brain injury
TNF-alpha	tumor necrosis factor-alpha
VaD	Vascular Dementia
WHO	World Health Organization

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