Epigallocatechin-3-Gallate (EGCG) Improves Cognitive Deficits Aggravated by an Obesogenic Diet Through Modulation of Unfolded Protein Response in APPswe/PS1dE9 Mice

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Epigallocatechin-3-gallate (EGCG), a catechin found in green tea, has been previously investigated for its neuroprotective effects in vitro and in vivo. In the present study, we aimed to evaluate its possible beneficial effects in a well-established preclinical mixed model of familial Alzheimer?s disease (AD) and type 2 diabetes mellitus (T2DM) based on the use of transgenic APPswe/PS1dE9 (APP/PS1) mice fed with a high fat diet (HFD). C57BL/6 wild-type (WT) and APP/PS1 mice were used in this study. APP/PS1 mice were fed with a palmitic acid?enriched HFD (APP/PS1 HFD) containing 45% of fat mainly from hydrogenated coconut oil. Intraperitoneal glucose tolerance tests (IP-GTT) and insulin tolerance tests (IP-ITT) were performed. Western blot analyses were performed to analyse protein expression, and water maze and novel object recognition test were done to evaluate the cognitive process. EGCG treatment improves peripheral parameters such as insulin sensitivity or liver insulin pathway signalling, as well as central memory deficits. It also

markedly increased synaptic markers and cAMP response element binding (CREB) phosphorylation rates, as a consequence of a decrease in the unfolded protein response (UPR) activation through the reduction in the activation factor 4 (ATF4) levels and posterior downregulation of protein tyrosine phosphatase 1B (PTP1B). Moreover, EGCG significantly decreased brain amyloid ? (A?) production and plaque burden by increasing the levels of ?-secretase (ADAM10). Also, it led to a reduction in neuroinflammation, as suggested by the decrease in astrocyte reactivity and toll-like receptor 4 (TLR4) levels. Collectively, evidence suggests that chronic EGCG prevents distinct neuropathological AD-related hallmarks. This study also provides novel insights into the metabolic and neurobiological mechanisms of EGCG against cognitive loss through its effects on UPR function, suggesting that this compound may be a promising disease-modifying treatment for neurodegenerative diseases.

APPswe/PS1dE9 mice

Cognitive deficits

Epigallocatechin-3-gallate

Hippocampus

Obesity

Unfolded protein response

activating transcription factor 4

ADAM10 endopeptidase

amyloid beta protein

cyclic AMP responsive element binding protein

epigallocatechin gallate

palmitic acid

protein tyrosine phosphatase 1B

toll like receptor 4

Alzheimer disease

amyloid plaque

animal experiment

animal model

animal tissue

Article

astrocyte

cognitive defect

controlled study

down regulation

drug distribution

glucose tolerance test

insulin sensitivity

insulin signaling

insulin tolerance test

lipid diet

male

memory disorder

Morris water maze test

mouse

nervous system inflammation

neuroprotection

non insulin dependent diabetes mellitus

nonhuman

novel object recognition test

obesogenic diet

protein expression

protein phosphorylation

synapse

unfolded protein response

Western blotting