The effects of Coenzyme Q10 in Transgenic Mouse Models of Alzheimer¡¦s Disease and Cerebral Ischemia: Volume MRI Study

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Introduction:

Coenzyme Q10 (CoQ10) is an essential biological cofactor which is produced endogenously and also acquired by dietary intake. It functions as an electron and proton carrier in the electron transport chain in mitochondria, and therefore has a crucial role in cellular energy production. Coenzyme Q10 supplementation increases brain mitochondrial concentrations and potential neruoprotective effects are being evaluated in a variety of conditions including familial amyotrophic lateral sclerosis and Parkinson's disease [1,2].

Amyloid precursor protein is involved in the response to a variety of experimental brain insults. Human mutations affecting metabolism of amyloid protein negatively impact outcome in a variety of transgenic mouse models of disease including Alzheimer's and stroke. Transgenic mice have been created which are singly transgenic for human amyloid precursor protein (APP), presenilin 1 (PS1), and doubly transgenic (APP-PS1). In an animal model of stroke, APP-PS1 mice ought to have worse outcomes than either single transgenic APP or PS1 mice. We tested two hypotheses in this study: 1) that in an experimental model of stroke, APP-PS1 mice would have greater cerebral ischemia than single transgenic APP or PS1 mice, 2) that CoQ10 would exert a neuroprotecive effect in stroke which differed by mouse genotype.

Materials and methods:

Transgenic mice expressing mutant human PS1 – Leu235Pro and APPswe were established at the National Institute of Environmental Health Science, NC3. Animals were 18 month old males (25g-30g) APP, PS1, and APP/PS1 mice (n = 36, 6 for each group). Focal cerebral ischemia was induced with a photothrombolic technique. A laser Doppler flowmeter was used to determine the cerebral blood flow (CBF) in ischemic penumbra[3]. Coenzyme Q10 (1200mg/kg/day) or its carrier vehicle (ie placebo) were given orally immediately after photothrombosis for 28 days after stroke. Then the mouse was deeply anaesthetized and transcardially perfused with 4% paraformaldehyde. On completion of the perfusion, the head of the animal was carefully removed and soaked in 4% paraformaldehyde. Fixed brain specimens were kept at 4 ºC prior to the MRI study.

MRI was performed on a Siemens Magnetom Trio 3 T whole body MRI at Sanatorium Hospital Hong Kong with a transmit/receive wrist coil. Parameters for 3D turbo spin echo (TSE) axial brain images were TR = 750 ms, TE = 113 ms, BW = 208 Hz/Px, FOV = 10 × 10cm, matrix size = 512 × 512, NEX = 2, slice thickness = 0.3 mm without slice gap. These were followed by 3D FLASH with the following imaging parameters: TR = 1500 ms, TE = 4.5 ms, BW = 130 Hz/Px, FOV = 16 × 10 cm, matrix 512 × 512, NEX = 5, slice thickness 0.2 mm without slice gap. ROIs of infarct volume (mm^3), dorsal hippocampus (DH), ventral hippocampus (VH), total hippocampus (TH) and hemisphere (HS) were calculated by manually delineating areas from 3D FLASH and TSE. Results were expressed as volume percentage from the volume of the ipsilateral hemisphere[4] as well as mean ± SE. The data were analyzed with one-way ANOVA test. The level of significance was set at $P<0.05$.

Results:

Relative CBF in the ischemic penumbra declined to 38.38±3.27% during 15 min. photothrombolic illumination and declined further to 33.38±2.27% at 30 min. after illumination in APP/PS1 mice. This was significantly lower than in either APP transgenic mice (15 min. 74.211±7.261; 30 min. 71.261±7.3113, $P<0.01$, n=6) or PS1 transgenic mice (15 min. 64.591±8.177; 30 min. 56.612±2.654, $P<0.01$, n=6). This result indicates that APP-PS1 mice suffered greater ischemia than either of the single transgenic strains.

The ratio of hemispheric size (HS - ischemic side vs non-ischemic side) in APP/PS1 transgenic mice with CoQ10 treatment, was significantly larger than in APP/PS1 transgenic mice receiving placebo ($P<0.01$, n=6). There was no significant difference in the ratio of HS (ischemic side vs non-ischemic side) between treatment and placebo groups in neither APP nor PS1 transgenic mice ($P>0.05$, n=6). There was no significant difference ($P>0.05$, n=6) in the relative infarct volume (IFV) between palcebo and CoQ10 treatment among the three different genotype strains. Stroke did not cause significant difference in the relative volumes of DH and VH between the ischemic side and non-ischemic side in three different genotype strains. Also, there was no significant difference in the relative volume of TH between pacebo and treatment groups ($P>0.05$, n=6) in the three different genotype strains. Fig. 1 shows MRI of brain specimen of APP/PS1 transgenic mice without CoQ10 treatment (A) and with CoQ10 treatment (B)

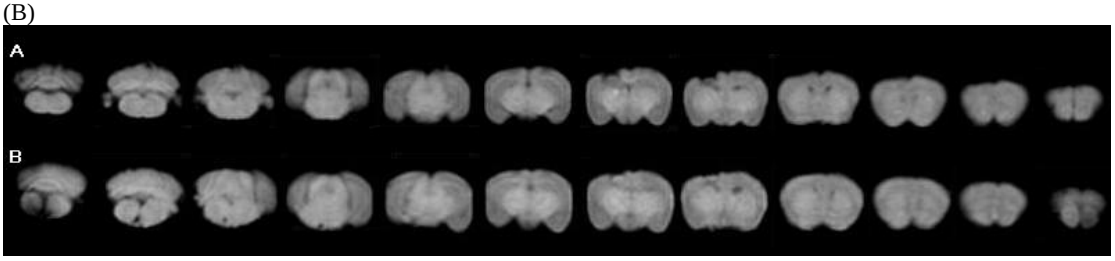

Fig. 1. MRI transverse slices of brain specimen of APP/PS1 transgenic mice. (A) an example of placebo group. (B) an example of treatment group.

Discussion:

In comparison with APP and PS1 transgenic mice, the relative CBF in ischemic penumbra was lower in APP/PS1 transgenic mice. This indicates that APP/PS1 transgenic mice are more susceptible to photothrombotic stroke than single transgenic APP or PS1 transgenic mice. While we found no significant difference in the relative infarct volume between the pacebo and treatment groups, hemispheric volume in the treatment group was preserved to a greater extent in the treated than placebo animals. This was true only in the strain (APP-PS1) which displayed the greatest vulnerability to ischemic damage. This result demonstrates that CoQ10 may protect ischemic tissue from atrophy.

References:

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