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Neurological Disorders Article Breakdown - Alzheimer's and Aging

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1. What were the justifications for this study?

Alzheimer's disease, commonly abbreviated as AD, is the most common form of dementia and progressive neurodegenerative disease.

The precise molecular mechanisms underlying the effect of physical exercise on the inhibition of Aβ production are not yet fully understood.

Treadmill exercise regulates APP or the amyloid precursor protein processing in the non-amyloidogenic pathway.

The molecular mechanisms inhibiting Aβ production through SIRT-1 mediated-APP processing after treadmill exercise in AD are still unclear.

SIRT-1 activation by caloric restriction may activate ADAM-10 via downregulation of Rho-associated kinase 1 also known as ROCK-1 and thus increase the non-amyloidogenic pathway in AD mice.

2. What were the independent variables? What was the control?

NSE/APPsw Tg mice and their control non-Tg mice were divided into three groups at 12 months of age. These three groups were non-Tg sedentary mice (NTS, n = 8), Tg sedentary mice (TS, n = 8), and TG-treadmill exercise mice (TE, n = 8). Tg stands for transgenic.

3. What methods were used to administer the IV?

Treadmill exercise at 10 m/min for 10 min/day for 5 days so that the mice would become familiar with the exercise environment. After this training period, treadmill exercise was performed at 10 m/min for 30 min/day for 5 days every week in the first 2 weeks and 50 min/day for the second two weeks. TE mice were then performed at 12 m/min for 50 min/day for 5 days/week in the third 3 weeks and the last 5 weeks of exercise were performed at 12 m/min for 60 m/day for 5 days a week.

4. What were the dependent variables?

Levels of Aβ-42, Aβ-40, m-cyto c protein, c-cyto c protein, and cleaved caspase-3 were all measured in % of sedentary. The m-cyto c/c-cyto c ratio may be a derived dependent variable. The number of TUNEL positive cells were

measured. Escape latency was measured in seconds and escape distance was measured in meters. The number of crossings was measured. The dwelling time in the target quadrant was measured in seconds. The amount of SIRT-1 was measured in percent in correlation with Aβ-42 percent levels. The amount of RARβ protein and ROCK-1 protein were both measured in % of sedentary. RARβ and ROCK-1 levels were measured in percent and were correlated with SIRT-1 percent levels. The amount of ADAM-10 protein was also measured in % of sedentary. The amount of APP protein, sAPPα protein, sAPPβ protein, CTFα protein, and CTFβ protein were all measured in % of sedentary. The amount of PGC-1α protein, BACE-1 protein, and C-99 protein were all measured in % of sedentary. The amount of PCG-1α was also measured in percent and correlated with SIRT-1 percent levels.

5. Describe how each DV was measured and for what the DV was a proxy.

For the western blot experiments (n = 5/group), the mice were euthanized by carbon dioxide asphyxiation and their cortex was separated from the brain on ice after the treadmill exercise. The samples were homogenized and the protein levels were assessed using a kit.

For immunohistochemistry experiments (n = 3/group), the mice of each group were perfused with a phosphate buffer saline followed by paraformaldehyde in a sodium phosphate buffer.

6. State each of the specific hypotheses used in this study.

If NSE/APPsw Tg mice were exposed to the treadmill exercise treatment, then Aβ levels would be reduced compared with mice without treadmill exercise.

If NSE/APPsw Tg mice models were exposed to the treadmill exercise treatment, then there would be less Aβ-induced cell death compared to mice without treadmill exercise.

If NSE/APPsw Tg mice were exposed to treadmill exercise, then spatial learning and memory function would be improved compared to that of mice without treadmill exercise.

If NSE/APPsw Tg mice were exposed to treadmill exercise, then SIRT-1 expression would be increased compared to that of mice without treadmill exercise.

If NSE/APPsw Tg mice were exposed to treadmill exercise, then ADAM-10 expression would be increased compared to that of mice without treadmill exercise.

If NSE/APPsw Tg mice were exposed to treadmill exercise, then there would be decreased APP β-cleavage and increased APP α-cleavage compared to that of mice without treadmill exercise.

7. List the results which support or disprove the hypotheses.

The levels of Aβ-42 and Aβ-40 were significantly higher in TS mice than in NTS mice and this increase was significantly reduced after treadmill exercise in TE mice. ($p < 0.001$)

There were significant decreases in m-cyto c levels and increases in c-cyto c levels in TS mice compared with NTS mice, whereas treadmill exercise increased m-cyto c levels and decreased c-cyto c levels in TE mice. ($p < 0.001$)

Both escape latency and escape distance were significantly decreased and increased respectively in TE mice when compared to TS mice without treadmill exercise. ($p < 0.001$ or $p < 0.05$)

SIRT-1 activity was significantly decreased in TS mice compared to NTS mice and it significantly increased after treadmill exercise in TE mice. ($p < 0.001$)

TS mice showed significantly decreased levels of RARβ and significantly increased levels of ROCK-1 compared to NTS mice, whereas RARβ levels were significantly upregulated and ROCK-1 levels downregulated after treadmill exercise in TE mice. ($p < 0.001$)

8. State the main conclusions.

Treadmill exercise might reduce Aβ production and improve cognitive deficits by increasing levels of ADAM-10 and decreasing BACE-1 levels via SIRT-1 activation and PGC-1α signaling.

The new insight provided by this study into the mechanisms of treadmill exercise-induced Aβ reduction may represent a potential therapeutic straight for AD in the future.

Treadmill exercise increases SIRT-1 levels through increasing ADAM-10 expression by downregulating ROCK-1 and upregulating RARβ. Treadmill exercise also increases PGC-1α levels which reduces BACE-1 and C-99 expression. All of this contributes to APP processing toward the non-amyloidogenic pathway.

9. State 2 or more (experimental design) limitations, either stated or not explicitly stated in the article.

A limitation of this study is that changes in the levels of AD-related proteins in NTS-exercise mice compared to NTS mice were not confirmed. Thus, the influence of genetic back-ground in the effects of treadmill exercise could not be clarified.

Another limitation is that they only measured the protein level of neuronal cell death-related factors. Therefore, it is insufficient to prove that neuronal cell death was due to Aβ.