P10

The Effects of rTMS on long-term potentiation and gene expression in transgenic 5XFAD mice

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Introduction

Repetitive transcranial magnetic stimulation(rTMS) is a safe and painless noninvasive brain stimulation technique that has recently received increasing interest as a therapeutic neurorehabilitative tool. Transcranial magnetic stimulation(TMS) is fragmentarily reported to be beneficial to Alzheimer's disease(AD). However little known about that high frequency rTMS is better than low frequency rTMS in AD.

Objective

The aim of this study was to investigate effect of rTMS on long-term potentiation(LTP) in Alzheimer's dementia mice model(5X FAD) depends on frequency and to analyze the different biomechanical change in gene level using RNA sequencing technology.

Method

Fifteen Male transgenic mice (16-22 weeks old, 5X FAD) and fifteen age-matched Male C57BL/6J wild type model mice were used for experiments. Experimental mice were divided to 3 groups of five mice each according to the experimental schedule in order; control group (sham treatment), low frequency(LF) group (1Hz) and high frequency(HF) group (5Hz). The rTMS (intensity, 120% of RMT; duration, 10s; number of pulses, 50; wait time, 60s; number of trace, 10) was applied at 1 or 10Hz five days a week for 2 weeks to AD model mice (FAX5D), while the control group was treated with sham rTMS. All mice were sacrificed and brain tissues in hippocampus were taken and hippocampal LTP was tested within 2 days after the completion of rTMS schedule. We analyzed their gene expression by RNA sequencing technology.

Results

1) LTP in the HF group (149.8±3%) was shown to be significantly enhanced than LTP in the LF group (116.7±3%) compared to control group. There was no significant difference in wild type group after the 1-Hz rTMS protocol and 5-Hz rTMS protocol. 2) Activation of p-GSKβ(s9) was significantly increased in AD model mice after 5-Hz rTMS. There were no significant differences in activation of Caspase-3 expression between HF group and LF group. 3) We found out the significant fold changes ($p<0.05$, fold change > 2 times, average of normalized read count (RC) > 4 times) in 4 genes (Grip1 ,Vwc2, Rom1 and Trp73) related to neurogenesis in LF group and 2 genes (Fmn1 and Naglu) in HF group. There was no overlapped up-regulated or down-regulated gene related to neurogenesis between LF group and HF group. 4) There was significant fold change in 2 genes related to aging in HF group compared with control group. Serping1 gene was up-regulated and

Serpine1 gene was down-regulated. 3) Serpine1 gene was significantly down-regulated in high-frequency group compared with control group. There was no significant fold change in any gene related to angiogenesis in low-frequency group compared with control group.

Conclusion

High-frequency rTMS significantly enhanced long-term potentiation in Alzheimer's dementia mice model. Moreover, There is a possibility that the mechanism is high-frequency rTMS-induced down-regulation of SERPINE 1 gene.

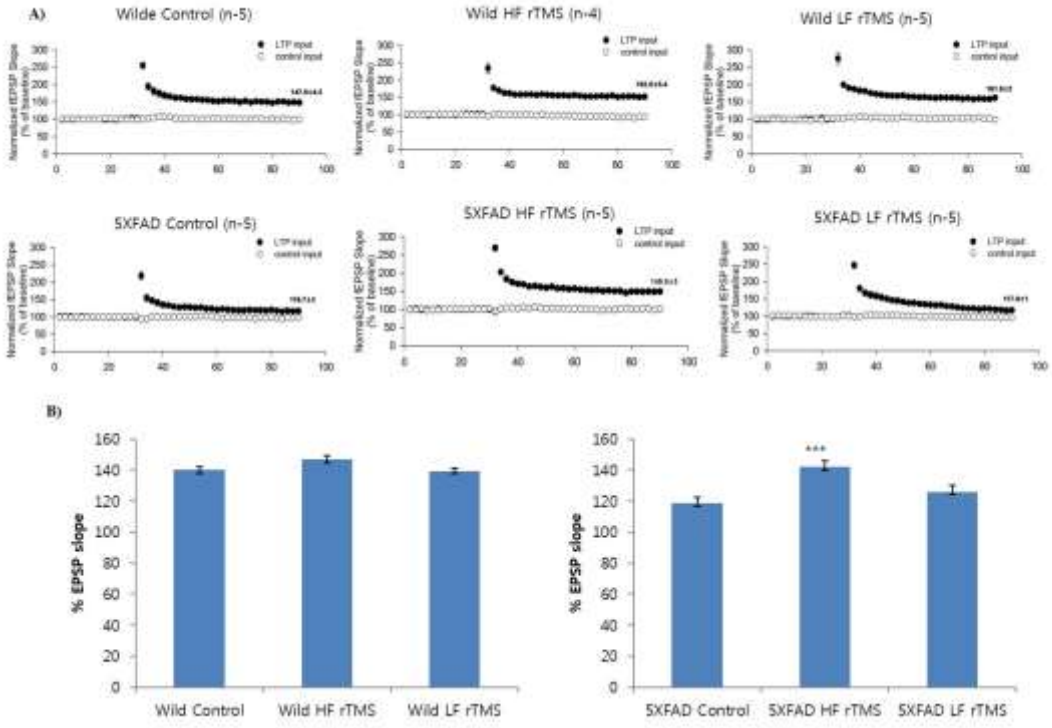

Fig 1. Effects of repetitive transcranial magnetic stimulation depends on frequency

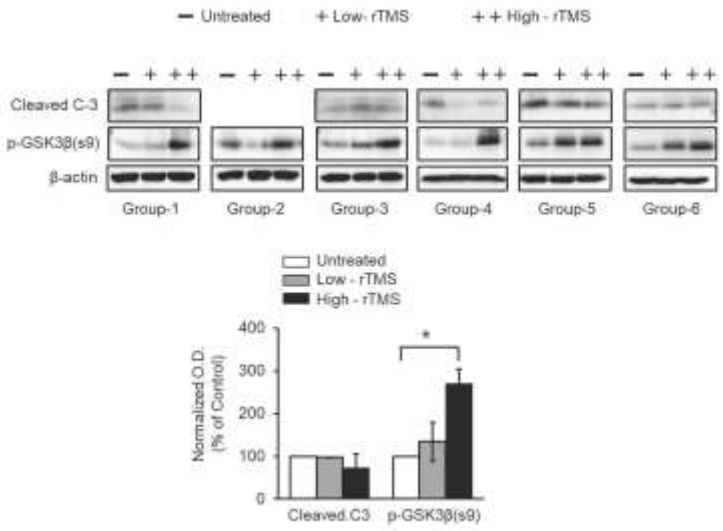

Fig 2. Activation of Cleaved C-3 and p- p-GSKβ(s9)

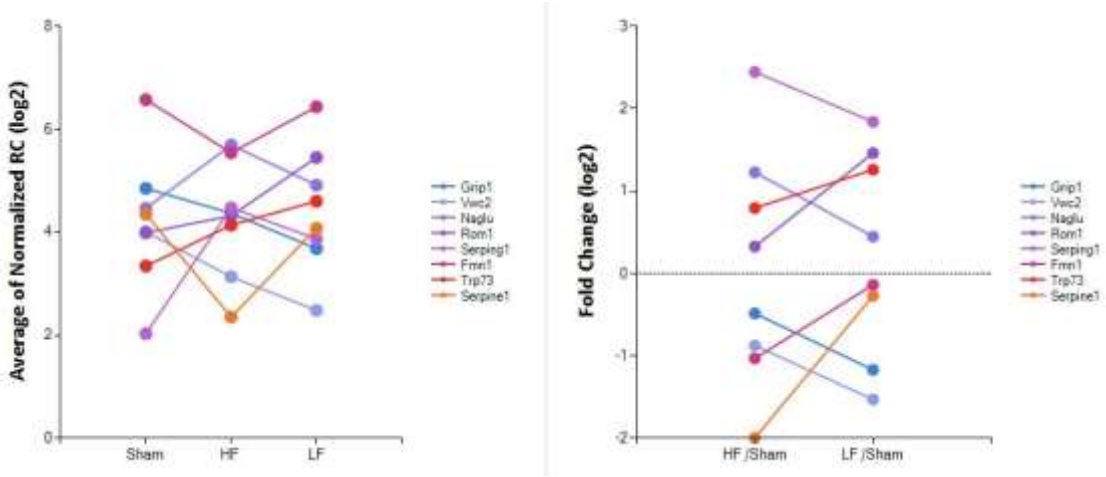

Fig 3. High frequency rTMS-induced Down-regulation of SERPINE1 gene Expression