Enhancing brain plasticity to contrast clinical progression in MS: a pilot study assessing the safety and efficacy of D-Aspartate

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Introduction

In progressive MS irreversible disability accumulates with neurodegenerative damage. Synaptic plasticity, the brain capacity to potentiate or depotentiate trans-synaptic neuronal transmission is altered.

Using TBS, a TMS protocol able to induce LTP, PPMS patients showed defective LTP in comparison with RRMS patients and healthy controls, suggesting that PPMS is associated to reduced synaptic plasticity reserve. The occurrence of LTP at individual synapses is mainly under control of the NMDAR. We thus considered NMDAR agonists as a potential path to enhance LTP induction. D-Aspartate (D-Asp), a substance commercialized and approved for the use in humans as a dietary supplement, modulates NMDA receptors function, and enhances LTP induction in rodents

Aim of the study

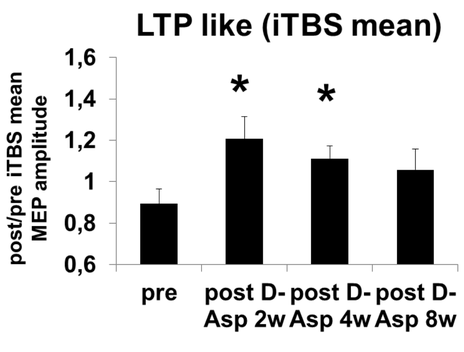
To explore whether D-Asp is safe, and effective in enhancing LTP response in PPMS patients.

Methods

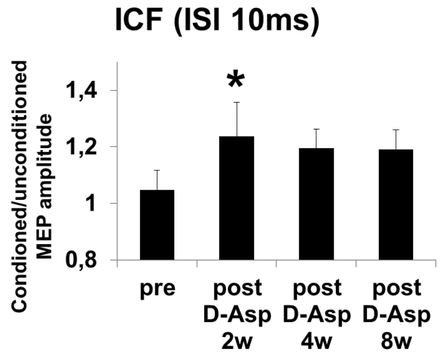
In 20 patients with diagnosis of PPMS we measured glutamatergic synaptic transmission through paired-pulse TMS protocols (SICI, ICF, SICF), LTP through iTBS, clinical disability through the EDSS and MSFC and, fatigue through the FSS before and after administration of single oral daily doses of D-Asp 2660mg for 4 weeks. TMS measurements were performed at baseline, 2, 4, and 8 weeks after treatment. Clinical measurements were performed at baseline, 12 and 24 weeks after treatment. Adverse events and safety monitoring were also recorded at baseline 2, 4, and 8 weeks after treatment.

Results and TMS assessments

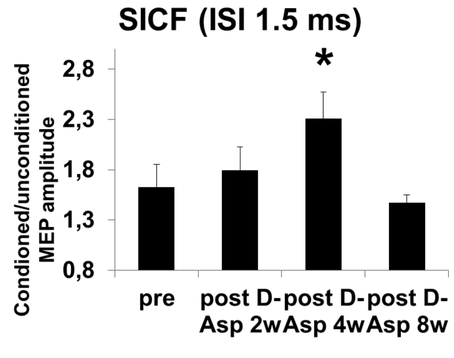
No adverse reactions were reported



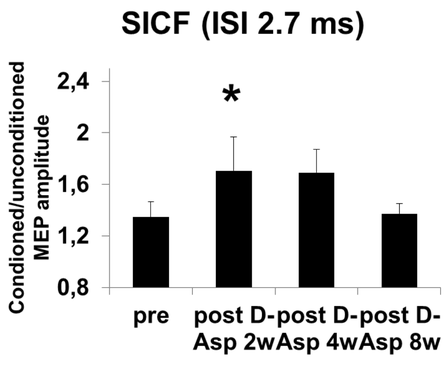
LTP increased after D-Asp p<0.05



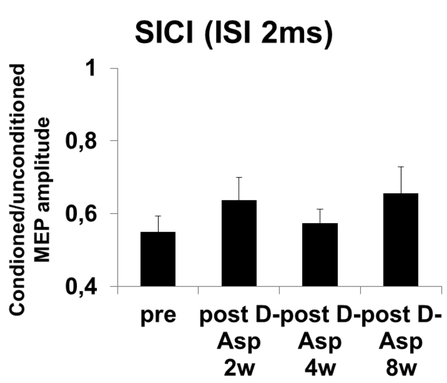
Intracortical facilitation (ICF) mediated by glutamatergic receptors increased after D-Asp p=0,043



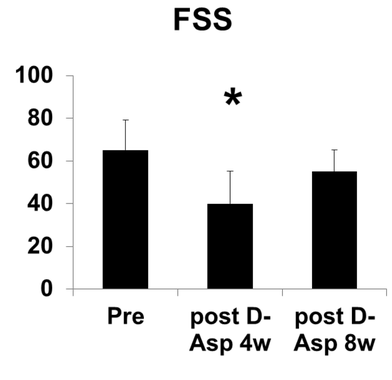
Short-interval intracortical Facilitation (SICF) at 1.5ms interstimulus interval mediated by glutamatergic receptors increased after D-Asp p=0.029



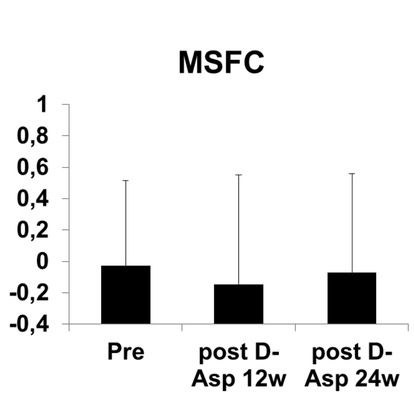
Short-interval intracortical Facilitation (SICF) at 2.7ms interstimulus interval mediated by glutamatergic receptors increased after D-Asp p=0.047

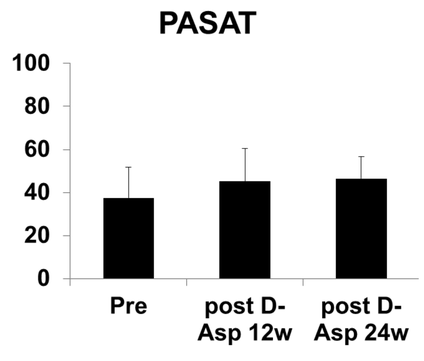


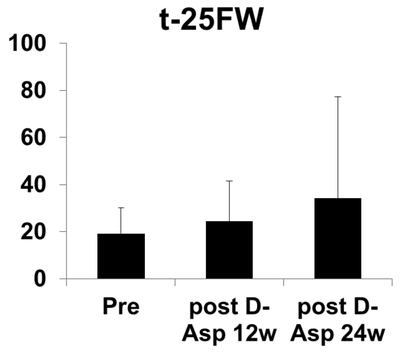
Short-interval intracortical inhibition (SICI) mediated by GABA-A receptors did not change after D-Asp

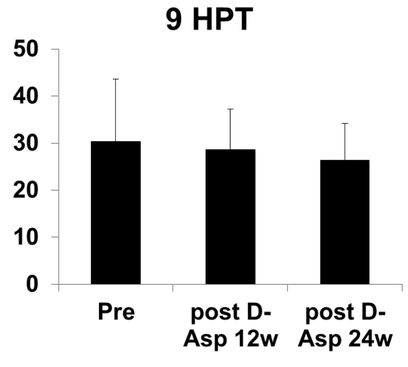


FSS scores improved after D-Asp p=0,039









Conclusion

D-Asp prove safe and effective in restoring brains plastic properties in primary progressive MS.

As expected, there were no changes in any clinical score, except decrease of fatigue tested by FSS.

This will open the path to a successive phase of the study where D-Asp clinical effects will be tested on progression of disability in progressive forms of MS.

It could be a unique therapeutic opportunity that might be provided for people with progressive forms of MS which, so far, have no therapeutic options to delay disease progression.

References

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