D-ASPARTIC ACID AMELIORATES COGNITIVE IMPAIRMENT IN A MOUSE MODEL OF SPARED NERVE INJURY AND REDUCES B-AMYLOID AB1-40 AND AB1-42 PEPTIDES

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D-aspartate (D-Asp) is a free D-amino acid found in the mammalian brain and it is the putative precursor of endogenous N-methyl-D-aspartate (NMDA) (1) activates itself NMDA receptors (NMDARs) on the orthosteric site with a relatively high affinity on each NR2A-D receptor subunits (2,3). Furthermore, it is involved in neurological and psychiatric processes, such as cognition and affective disturbances. Depressive symptoms and other neuropsychiatric dysfunctions are common in neurodegenerative disorders, including chronic pain and dementia. A correlation between the β-amyloid protein accumulation and depression development has been suggested, however the underlying mechanisms are unknown.

Based on these evidence, our study aimed to investigate the effects of this amino acid on pain responses and pain-related affective and cognitive behaviour; the presence and the effect of D-Asp treatment on the soluble β-amyloid Aβ1-40 and Aβ1-42 peptides in the serum, in the medial frontal cortex (mPFC) and in the hippocampus in a long lasting model of neuropathic pain; and the levels of testosterone, progesterone and 17β-estradiol in the brain.

We have validated this hypothesis using a combination of immunoenzymatic and behavioral approaches in Sham and SNI (Spared nerve injury) mice, a model of neuropathic pain (4), 1 year post-surgery. Moreover, we examined the effects of D-Asp (20 mM) in drinking solution for 1 month.

In a long lasting model of neuropathic pain, SNI mice showed mechanical allodynia, anxiety and depression-like behaviour and cognitive impairments. Moreover, we observed an increase of insoluble form of Aβ1-42 at hippocampal level and soluble form of Aβ1-40 at serum level.

D-Asp treatment improved mechanical allodynia, obsessive-compulsive and depressive-like behaviours and reduced the β-amyloid levels in the serum, mPFC, and hippocampus. Finally, D-Asp chronic treatment induced a significant increase of steroid hormones synthesis in the mPFC and hippocampus.

We found, for the first time, that the neuropsychiatric changes and pain behaviours observed in animals with long lasting peripheral neuropathy were associated with an overall increase of Aβ1-40 and Aβ1-42 peptides. D-Asp treatment reduced abnormal behaviours and normalized the β-amyloid protein level. Our findings provide new insights into chronic pain mechanisms and suggest a possible role of β-amyloid protein in neuropathic pain-associated neurological dysfunctions.

References

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