GLUTAMATE AND PSA-NCAM DEPENDENT HIPPOCAMPAL SYNAPTIC REMODELLING: CORRELATION WITH AN EXPERIMENTAL MODEL OF DEPRESSION AND ITS PHARMACOLOGICAL TREATMENT

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INTRODUCTION
Dysfunction of hippocampal plasticity and excessive glutamate (GLU) release has been proposed to play a critical role in the pathophysiology of depression. In experimental models of depression such as the learned helplessness paradigm (LH), hippocampal dendritic atrophy has been reported. We have previously shown in hippocampal CA3 region of LH animals decreased synaptic proteins PSD-95 and synaptophysin (SYN) and that chronic treatment with fluoxetine (FLX) reverses the behavioral deficit and recovers PSD-95 and SYN levels, pointing out the synapse as a target for antidepressant action. Moreover, it is known that adhesion molecule NCAM (Neural Cell Adhesion Molecule), one of the most abundant in glutamatergic synapses, contributes to hippocampal plasticity.

MATERIALS AND METHODS
We examined synapse morphology and cell adhesion molecule (CAM) expression in animals subjected to the LH paradigm: control animals that received no shock (C), shocked non depressed animals (SND) and shocked animals that showed the behavioural deficit (LH). We studied the effect of 21 day treatment with FLX employing four groups: control animals treated with saline (C-S) or fluoxetine (C-FLX) and LH animals that received saline (LH-S) or fluoxetine (LH-FLX). While CA3 synaptic morphology was analyzed by electronic microscopy, adhesion molecule expression was determined by Western blot and immunohistochemistry. Glutamatergic hyperstimulation effects on adhesion molecules and cytoskeletal, pre- and post-synaptic proteins were analyzed in primary neuronal cultures by immunohistochemistry.

RESULTS
Concerning electronic microscopy, CA3 synapses of LH animals showed increased synaptic cleft width. While in control rats synaptic vesicles per synapse (SV/S) ratio was homogenous, in LH group SV/S ratio presented extreme low or high values. Postsynaptic density (PSD) morphology was altered in LH rats: while PSD length decreased, PSD width increased rendering similar values in total area. These results are compatible with plastic and synaptic connectivity alterations. LH rats showed decreased immunostaining for CA3 NCAM and PSA-NCAM (NCAM polysialylated non-adhesive form). Glutamate hyperstimulation of hippocampal neurons in culture decreased immunostainings of the dendritic marker MAP2, NCAM and PSA-NCAM. It also diminished PSD-95(+) and SYN(+) synapse number and increased SYN(+) individual synapse area. Our results indicate that excessive neuronal exposure to GLU induces synaptic changes in vitro that resemble those observed in LH animals. FLX treatment of LH animals returned synaptic cleft width to control values and increased reserved synaptic vesicle number. Regarding cell adhesion molecules, FLX strongly reduced CA3 NCAM expression and most importantly, increased CA3 PSA-NCAM levels in LH rats.

CONCLUSIONS
Results support the hypothesis that GLU hyperactivity in the CA3 of LH rats could reduce CAM expression leading to alterations in synaptic connectivity. Since PSA-NCAM is considered a neuronal plasticity marker it can be suggested that fluoxetine action in LH animals may involve PSA-NCAM dependent synaptic remodelling that might lead to neuronal connectivity normalization.

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