INTRODUCTION

Deep Brain Stimulation (DBS) in the subgenual cingulated (Cg25) has revealed as a new and promising innovative technique that may be able to provide sustained remission in resistant major depressive disorder. The first clinical series have reported an initial large effect followed by a decay in the first month of treatment. However, this unexpected phenomenon, attributed to a potential placebo effect or a physiological response to probe insertion, remains poorly understood.

MATERIAL AND METHODS

Male Wistar rats weighing 200–250 g. The electrodes of stimulation were implanted bilaterally into the infralimbic cortex (the rodent Cg25 correlate). The stimulation protocol was 100 µA, 130 Hz and 90 µsec (Haman et al.2010). The modified Forced Swimming Test (mFST) were used as a model predictive of antidepressant-like effect (Detec et al. 1995). Spontaneous locomotor activity was also analyzed.

Immunohistochemistry procedure were performed against GFAP (Glia fibrillary acidic protein), MAP2 (neuronal marker) and p11 (S100-A10) in vmPFC. Western blot procedure were performed against p11 (S100A10) and α-tubulin in vmPFC.

Statistical analysis. Mean ± SEM. One or two-way ANOVA followed by Bonferroni test. Significant values were considered when p < 0.05.

Drugs. Imipramine (15 mg/kg, i.p., 1/5h after pre-test and 2h before test for behavioural studies and once daily for 14 days for western blot assay); para-chlorophenylalanine methyl ester (pCPA, 100 mg/kg, i.p, 3 days before test); indomethacin (INDO, 1 mg/kg, i.p.) and ibuprofen (50 mg/kg, p.o.) both once daily from 2 days before the surgery until the mFST.

Clinical studies. The clinical trial was comprised 8 patients with resistant major depression underwent DBS in Cg25. Clinical outcome of the first month of Cg25 DBS in patients was quantified. Depressive symptoms were rated according to the HDRS-17.

RESULTS

PRECLINICAL STUDIES Antidepressant-like effect of DBS and electrode implantation in IL cortex in mFST. This effect is not due to changes on spontaneous locomotion and is mediated by the serotonergic system.

The electrode implantation increased expression of p11 (S100A10) in vmPFC neurons

The effect of electrode implantation was self-limited over the time.

Anti-inflammatory treatment blocked the antidepressant-like effect of electrode implantation.

CLINICAL STUDIES Analgesic-antiinflammatory treatment after the surgery blocked the early antidepressant effect of DBS.

CONCLUSIONS

This study demonstrates that electrode implantation in the IL cortex is sufficient to produce an antidepressant-like effect mediated by the serotonergic system. This effect appears to be transient and it is accompanied by glial activation and an increase of neuronal p11 expression. In addition, it can be blocked by pre-treatment with the NSAIDs. These findings are correlated with the early effect observed in patients treated with DBS of Cg25, in whom surgery produced a significant improvement. Additionally, patients treated with NSAIDs exhibited a progressive increase in their HDRS scores. Overall, these findings rule out the potential influence of a placebo effect, suggesting that this initial antidepressant effect of DBS is the result of a beneficial local neuroinflammation provoked by electrode implantation.

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