THE IMPACT OF ANTIPSYCHOTIC DRUGS IN DEPRESSION: A ROLE FOR ADULT NEUROGENESIS?

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Introduction

Considering the crescent number of depressive patients and the increase of non-responders/incomplete responders to antidepressant treatment, it is essential to explore new strategies in order to achieve a full remission and to prevent recurrent depressive episodes. Recently, some atypical antipsychotic drugs have received FDA approval for the treatment of antidepressant-resistant forms of major depression. However, the mechanism triggered by these drugs remains widely undisclosed. Increasing adult hippocampal neurogenesis has been considered as an essential point involved in the therapeutic effectiveness of antidepressants. However, this same mechanism remains unexplored considering the actions of antipsychotics.

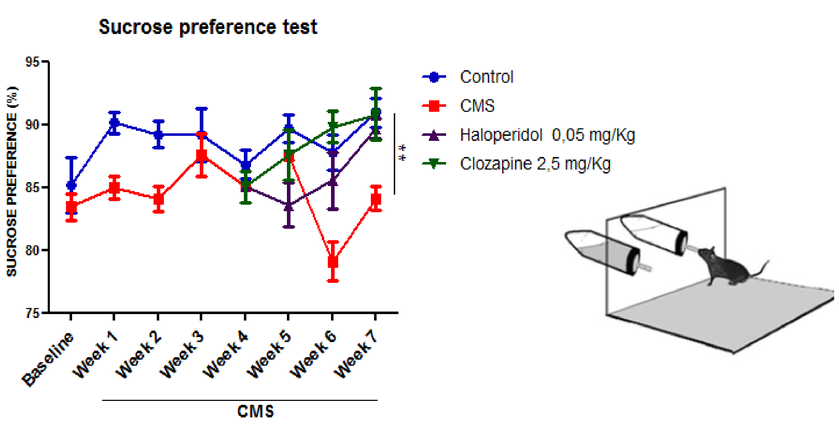
Methods

3-month old male Wistar rats were randomly assigned to four main experimental groups – a control group without stress exposure, treated with saline and three groups exposed to unpredictable chronic mild stress (uCMS) during 7 weeks and treated with either saline, clozapine or haloperidol (n = 8 per group) during the last three weeks of stress exposure. At the end of treatment, the behavioral dimensions commonly affected in depression were assessed and correlated with neurogenic alterations. Learned helplessness was evaluated in the forced swimming test (FST) and anxiety-like behavior was assessed in the elevated-plus maze test (EPM). Cognitive function was assessed by different tasks designed to assess spatial learning, working memory and behavioral flexibility in the Morris water maze (MWM) test. Anhedonia was assessed using the sucrose preference test.

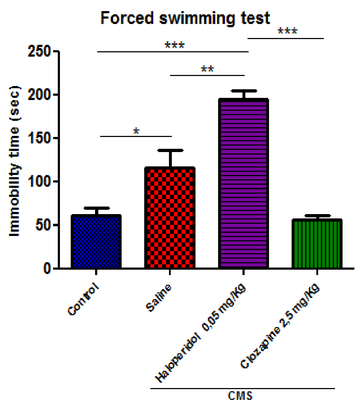
Results

Behaviour analysis

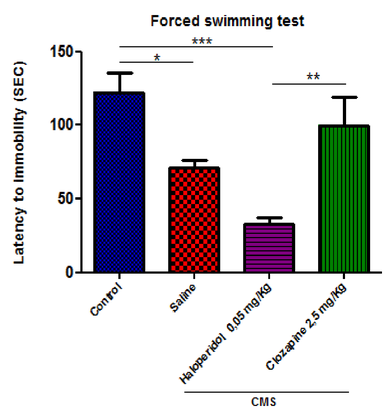
Effects on Mood



(**) p<0,01 CMS vs control , CMS vs Clozapine

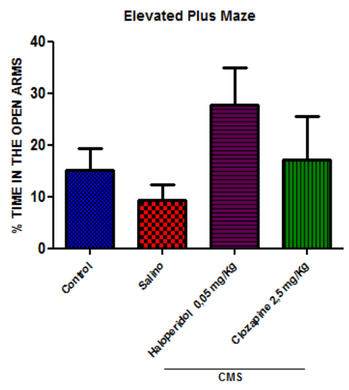


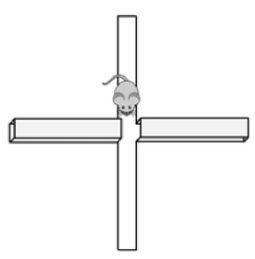
(*) p<0,05; (**) p<0,01; (***) p<0,001



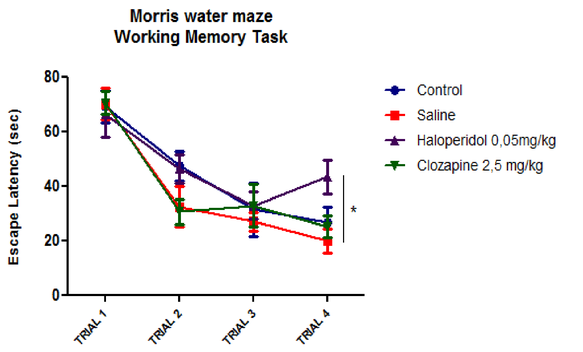
(*) p<0,05; (**) p<0,01; (***) p<0,001

Effects on Anxiety

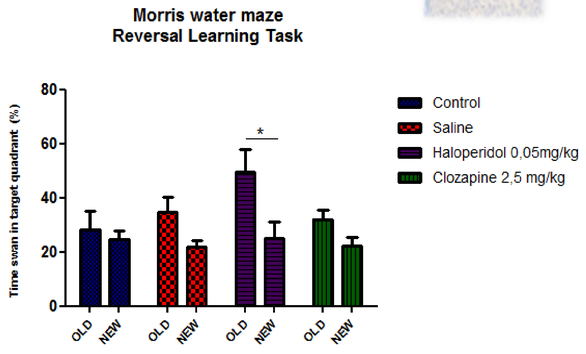




Effects on Cognition

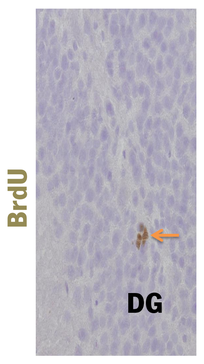


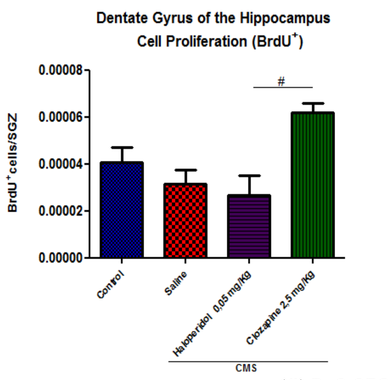
(*) p<0,01 CMS saline vs Haloperidol; Haloperidol vs Clozapine



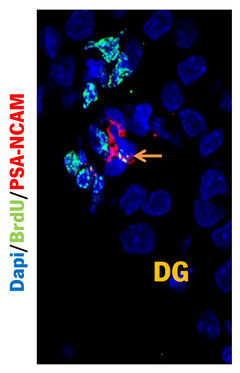
(*) p<0,05

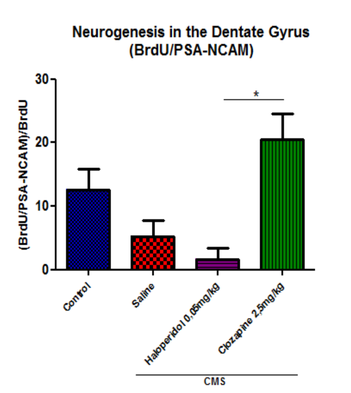
Immunostaining analysis



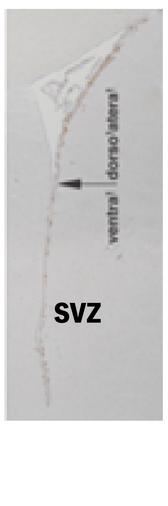


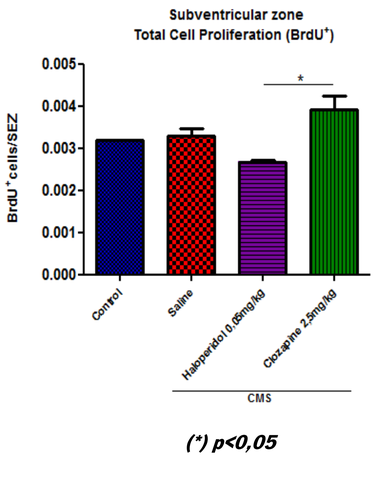
(#) P=0,056



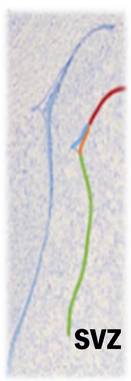


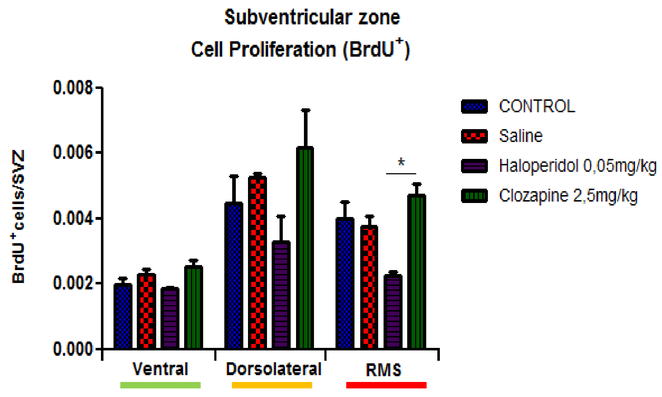
(*) p<0,05



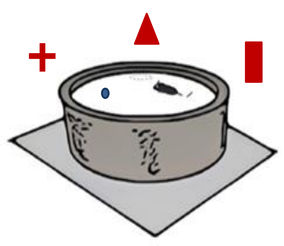


(*) p<0,05





(*) p<0,05



Conclusions

✓Clozapine reduces both measures of depressive-like behavior (learned helplessness and anhedonia). Haloperidol only reverted anhedonia phenotype and aggravated learned helplessness. Haloperidol-treated animals displayed cognitive impairments in the working memory and reverse learning task in the MWM test;

✓ Haloperidol and clozapine lead to different neuroplastic adaptive responses. Clozapine promotes cell proliferation and neurogenesis in the dentate gyrus of the hippocampus and in the subventricular zone. Contrastingly, haloperidol leads to a decrease in neurogenesis in these brain regions;

The present results suggest an association between the modulations of adult neurogenesis and the emotional/cognitive changes observed in response to different classes of antipsychotic drugs in an animal model of depression.

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