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

**Mónica Morais[1], António Pinheiro[1], Patrícia Patrício[1] , Nuno Alves[1], Luísa Pinto[1], Nuno Sousa[1], João M. Bessa[1]**

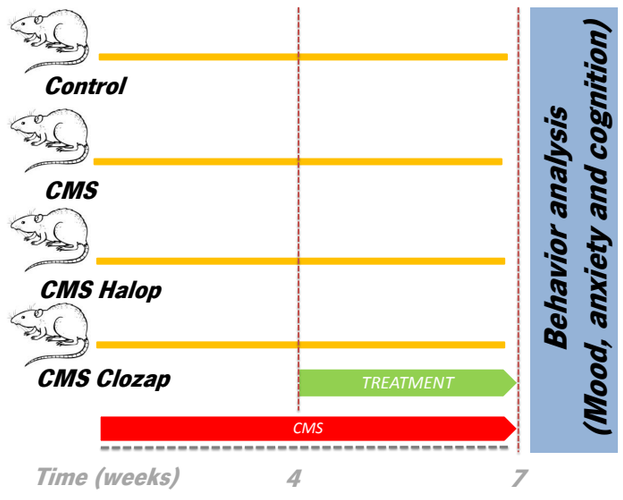
[1]Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Campus Gualtar, 4710-057 Braga, Portugal;
ICVS/3B's - PT Government Associate Laboratory, Braga/Guimarães, Portugal

## 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

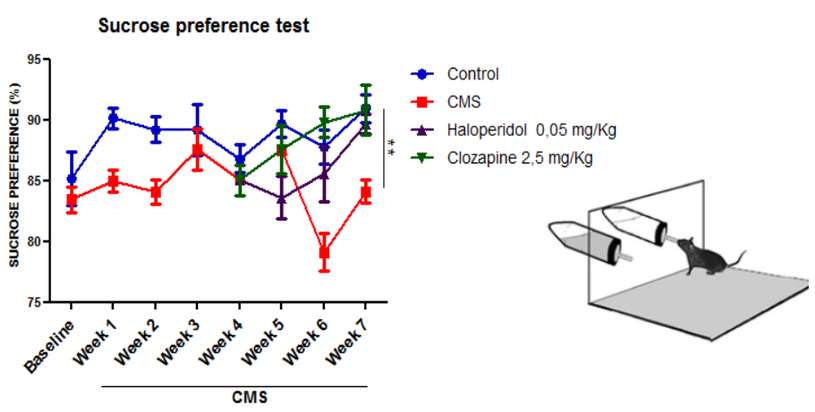
3-month old male Wistar rats were randomly assigned to four main experimental groups – a control group without stress exposure, treated with saline and three groups exposed to unpredictable chronic mild stress (uCMS) during 7 weeks and treated with either saline, clozapine or haloperidol ($n$ = 8 per 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.



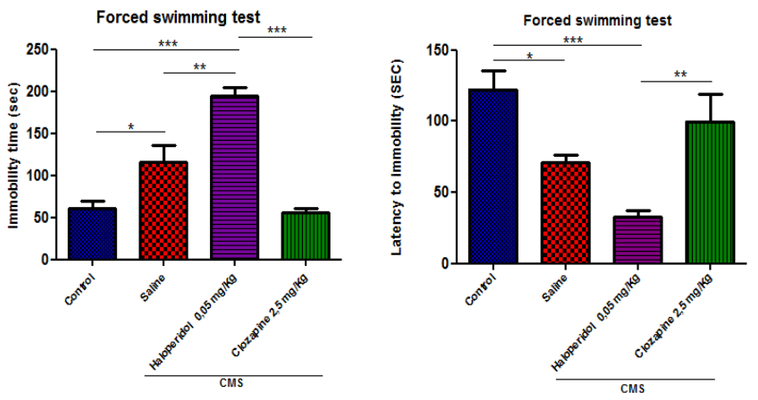

## Results

### Behaviour analysis

#### *Effects on Mood*



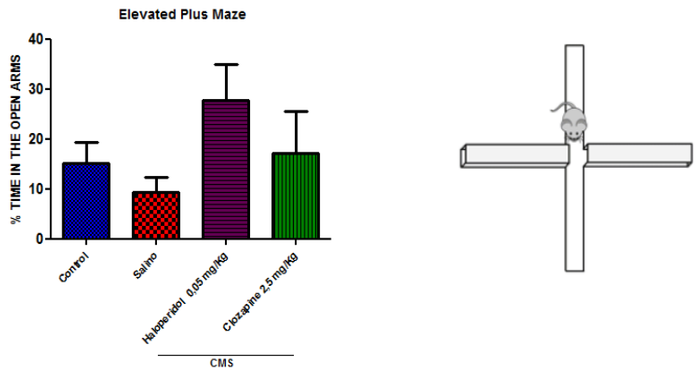

*(**) p<0,01 CMS vs control , CMS vs Clozapine*



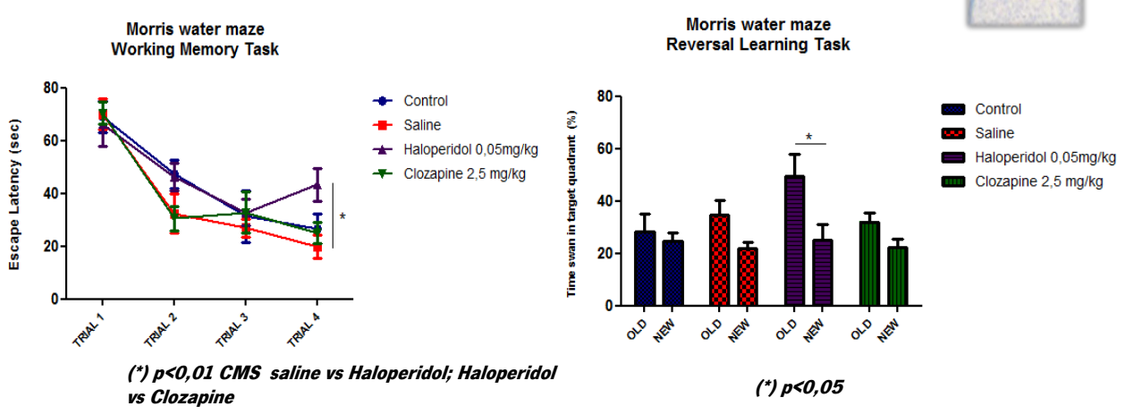

*(*) p<0,05; (**) p<0,01; (***) p<0,001*

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

#### *Effects on Anxiety*



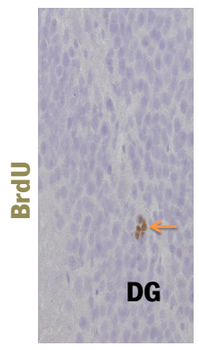

#### *Effects on Cognition*

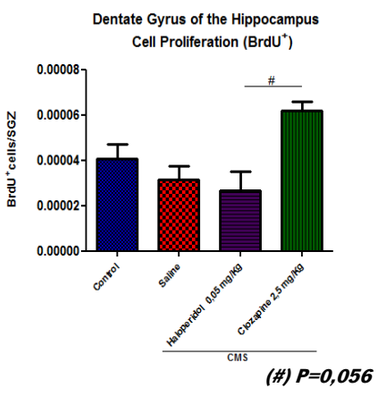



*(*) p<0,01 CMS saline vs Haloperidol; Haloperidol vs Clozapine*

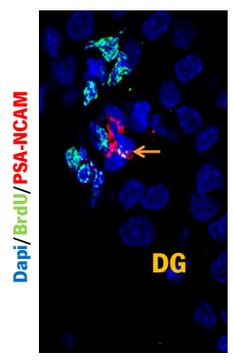
*(*) p<0,05*

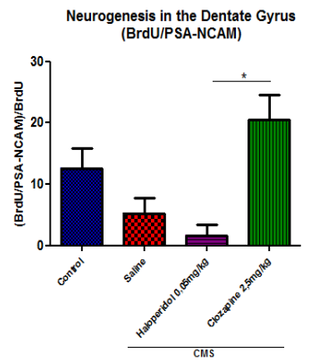
### Immunostaining analysis



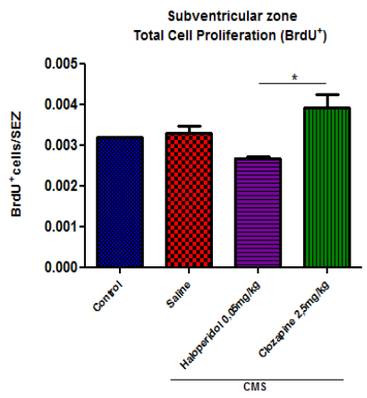




*(#) P=0,056*

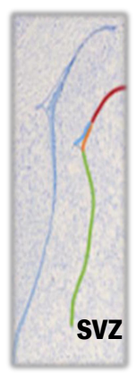


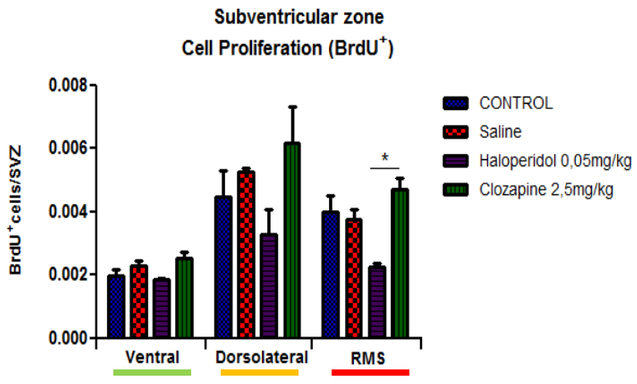




*(*) p<0,05*

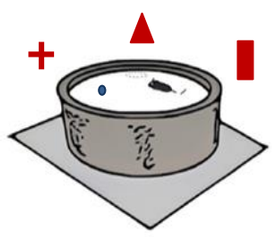




*(*) p<0,05*




*(*) p<0,05*




## Conclusions

✓Clozapine reduces both measures of depressive-like behavior (learned helplessness and anhedonia). Haloperidol 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 modulation 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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**The impact of antipsychotic drugs in depression: a role for adult neurogenesis?**

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*[1]Life and Health Science Research Institute, Neuroscience Research Domain, Braga, Portugal*

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 antidepressant. However, this same mechanism remains unexplored considering the actions of antipsychotics. To address these questions, an unpredictable chronic mild stress (uCMS) paradigm was implemented during 7 weeks to induce core symptoms of depressive-like behavior in rats [1]. During the last 3 weeks of uCMS, two antipsychotic drugs from different pharmacological classes, clozapine (2.5mg/kg) and haloperidol (0.05mg/kg), were daily administered [intraperitoneal injection (1ml/kg)]. 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, during all the experimental procedure [2]. After confirmation of homogeneity, appropriate statistical tests were applied to the data. Repeated measures ANOVA were used to analyze sucrose preference test and the spatial learning and working memory task in the MWM. Two-factor ANOVA was used to evaluate the remaining behavioral data as well as cell densities and immunostaining results. Differences between groups were then determined by Tukey's honestly significant difference test (Tukey HSD) post hoc analysis. Statistical significance was accepted for $P<0.05$. We found that treatment with clozapine reduces both measures of depressive-like behavior (learned helplessness and anhedonia) while haloperidol was able to revert the anhedonic phenotype but aggravated learned helplessness in the FST. Moreover, haloperidol-treated animals displayed cognitive impairments in the working memory and reverse learning task in the MWM test. These observations are in accordance with the differential clinical impact of these drugs in the negative symptoms of schizophrenia [3]. Our findings also suggest that 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 subependymal zone. Contrastingly, haloperidol leads to a decrease in neurogenesis in these brain regions. The present results suggest an association between the modulation of adult neurogenesis (hippocampus and subependymal zone) and the emotional and cognitive changes observed in response to different classes of antipsychotic drugs in an animal model of depression.

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**Keywords**

Animal behaviour

Depression: basic

Neuropharmacology