GALANIN (1-15) ENHANCES THE EFFECTS OF FLUOXETINE IN AN ANIMAL MODEL OF DEPRESSION. ROLE OF THE 5HT1A RECEPTOR.

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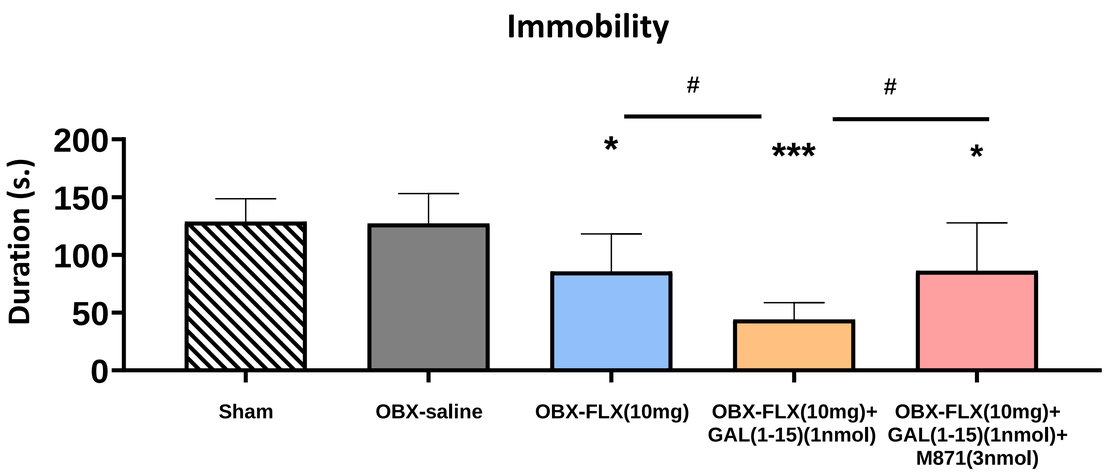
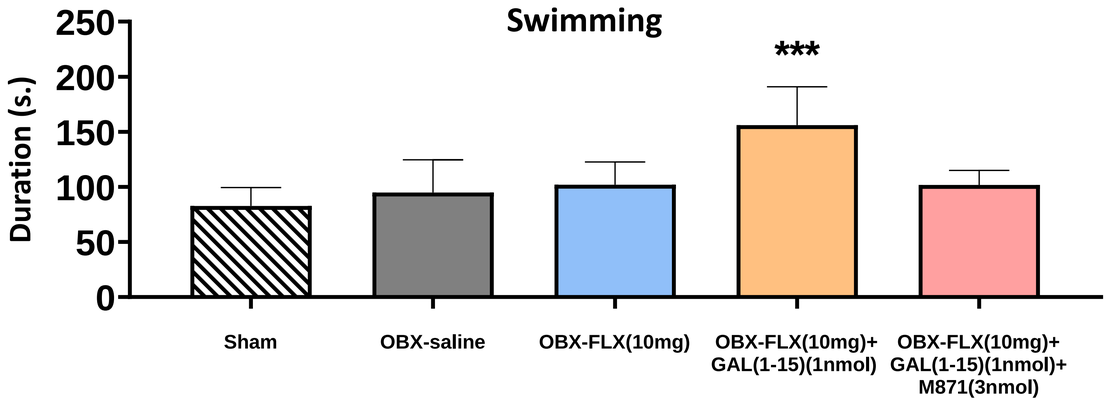
INTRODUCTION: Major depression is one of the most significant contributors to global disability. Selective serotoninergic reuptake inhibitors, including Fluoxetine (FLX), are the most commonly prescribed antidepressants for treating it. However, their effectiveness in remission is limited to only 30-50% of patients. In recent studies, we observed that the N-terminal fragment of Galanin [GAL(1-15)] enhanced the antidepressant effects of FLX in naïve rodents. In this study, we analyzed the effect of GAL(1-15) in combination with FLX in an animal model of depression, the olfactory bulbectomy (OBX) rats, in the forced swimming test (FST) and the sucrose preference test (SPT), which measure despair and anhedonic behaviours, respectively. We also studied the role of the hippocampal 5-HT1AR in GAL(1-15)-enhancing effects using saturation experiments with autoradiographic techniques.

MATERIAL AND METHODS: Groups of OBX rats (n=7-9) were administered with a subchronic treatment of FLX(10mg/Kg) alone or in combination with GAL(1-15)(1nmol) prior to the forced swimming test (FST) or sucrose preference test (SPT). FLX was administered subcutaneously at 23, 5 and 1 hour before the test, while GAL(1-15) was injected icv 15 minutes before the tests.
In the FST, two swimming sessions were conducted: a 15-minute pretest followed by a 5 minutes test 24 hours later. The duration of immobility, swimming and climbing behaviours were recorded during the second 5-minute sesión. The administration of drugs was performed between sessions. In the FST, we also studied the role of GALR2 using the antagonist M871, for this a group of rats was injected with the same administration pattern of FLX(10mg/Kg) in combination with GAL(1-15)(1nmol)+M871(3nmol) icv 15 min before the FST.
In SPT, during the test, rats were allowed free access to 2 bottles, one containing 1% (w/v) sucrose solution and the other containing tap water. After 2 hours, we weighed the bottles to calculate the sucrose intake and preference. Treatments were administered considering the beginning of the test 2 hours before weighing the bottles.
For autoradiographic experiments, brains (n=6) of FLX and GAL(1-15)+FLX-treated rats were removed, and coronal sections were obtained at the dorsal hippocampus. Saturation experiments were performed using [3H]-8-OH-DPAT; film exposure time for sections was six weeks.
All data were analyzed using GraphPad PRISM 8.0. For comparing more than two groups, One-way ANOVA followed by Fisher's least significant difference (LSD) comparison post-test was performed when the F ratio in the One-ANOVA was statistically significant. Differences were considered statistically significant at $P<0.05$.

BEHAVIOURAL RESULTS

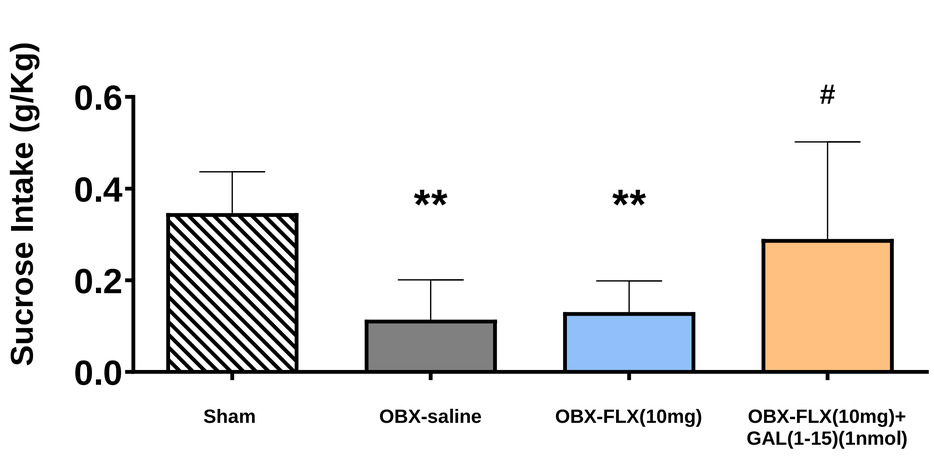
FST

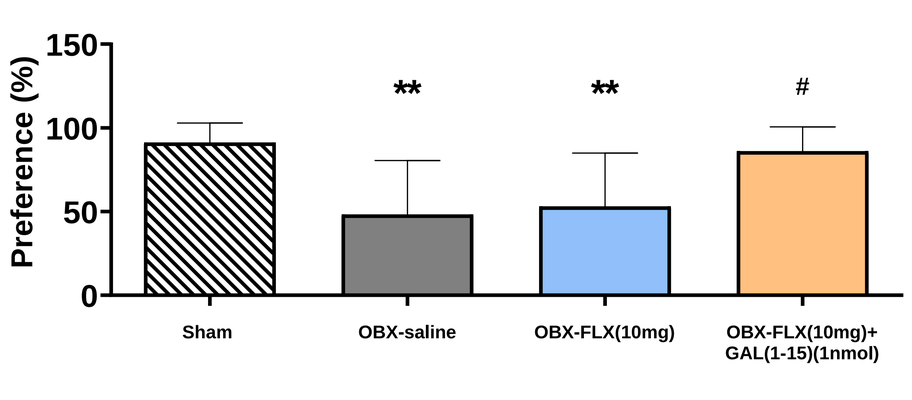




In the FST, GAL(1-15) enhanced the antidepressant-like effects mediated by FLX, decreasing the immobility time by 50% and increasing the swimming time by around 30%. M871(3nmol) blocked the GAL(1-15)-induced reduction of the immobility time and increased swimming time.
In Immobility *P <0 .05, ***P < 0.001 vs sham and OBX-saline groups; #P <0 .05 vs OBX-FLX (10 mg/kg)+GAL(1-15) (1 nmol);
In Swimming ***P <0 .001 vs rest of the groups according to one-way ANOVA followed by Fisher's least significance difference test.

SPT

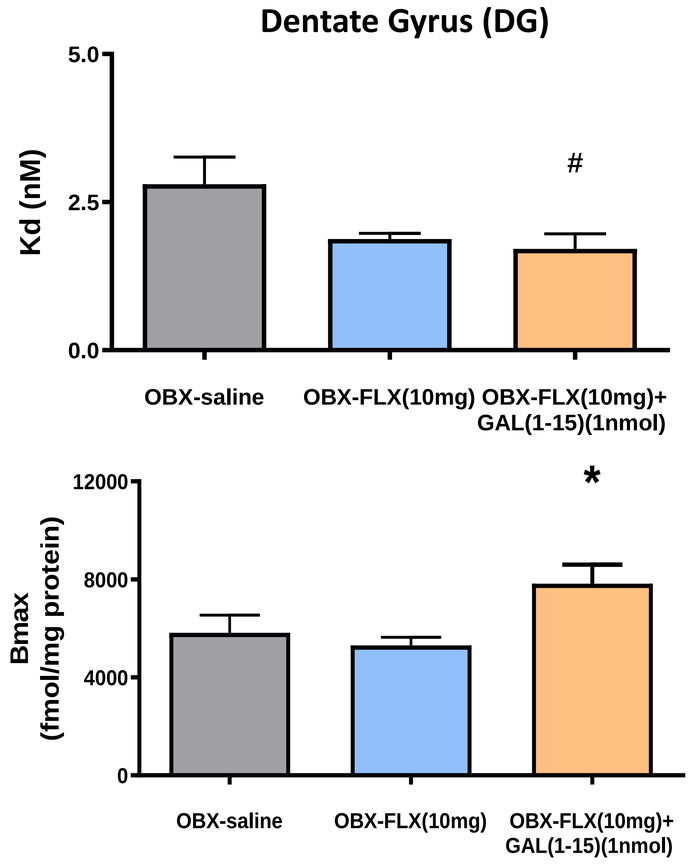


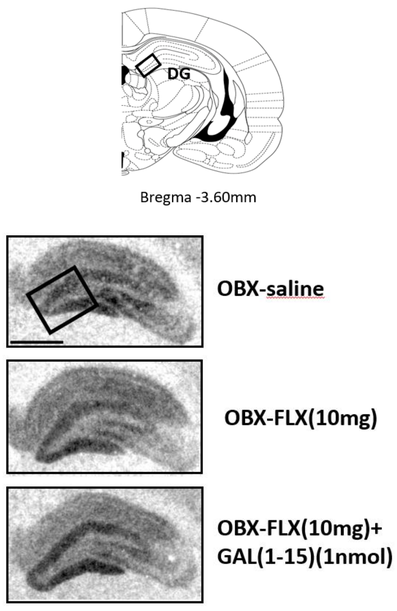


In SPT, OBX animals exhibited a reduction in sucrose intake and preference compared with sham animals. Only the coadministration of GAL(1-15)+FLX induced a statistically significant increase in sucrose intake and preference compared with the OBX-saline and OBX FLX-treated animals.
**P <0 .01 vs sham; #P < 0.05 vs OBX-Saline and OBX-FLX (10 mg/kg) groups according to one-way ANOVA followed by Fisher's least significance difference test.

AUTORADIOGRAPHIC RESULTS

Dentate Gyrus (DG)





Representative autoradiograms from the dorsal hippocampus sections of OBX animals show the increase of the 5-HT1AR agonist binding in DG with a high radioligand concentration (10nM).

The coadministration of FLX and GAL(1-15) produced a decrease in the Kd value compared with the OBX-saline group and a statistically significant increase in the Bmax value compared with OBX-saline and OBX-FLX groups. Therefore, only the coadministration of GAL(1-15)+FLX induced modifications in the binding characteristics of the 5HT1AR in the dentate gyrus of the dorsal hippocampus.
#P < .05 vs OBX-saline group and *P < .05 vs rest of the groups according to one-way ANOVA followed by Fisher's least significance difference test.

• CONCLUSIONS

1. GAL(1-15) enhances the antidepressant-like effects mediated by FLX in OBX rats in the FST.

2. The coadministration of FLX and GAL(1-15) reverts the effects of the OBX procedure in the SPT test.

3. The coadministration of FLX and GAL(1-15) modify the binding characteristics of the 5HT1AR radioligand [3H]-8-OH-DPAT in the DG region of the Dorsal hippocampus.

4. The results open the possibility of using GAL(1-15) in combination with FLX to treat depression.

Galanin (1-15) Enhances the Behavioral Effects of Fluoxetine in the Olfatory Bulbectomy Rat, Suggesting a New Augmentation Strategy in Depression.
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