New augmentation strategy in depression: Galanin(1-15) enhances the behavioral effects of Fluoxetine in the olfatory bulbectomy rat

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INTRODUCTION

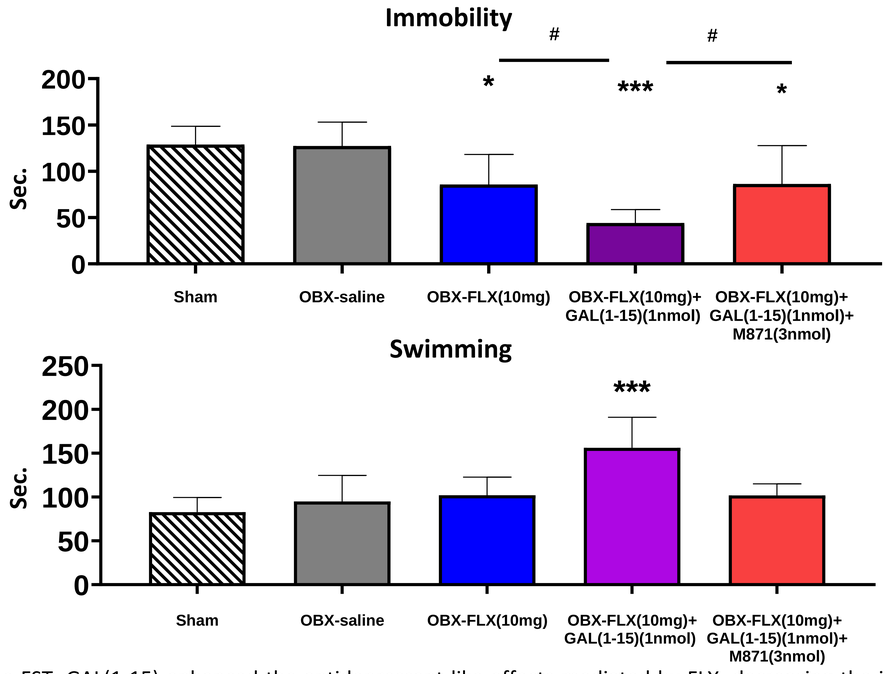
Major depression is the largest contributor to global disability by years lived with disability. Selective serotonergic reuptake inhibitors, including fluoxetine (FLX), are the most commonly used antidepressant for the treatment of major depression. However, they are effective for remission in only 30% of patients. Recently, we observed that the N-terminal fragment of Galanin [GAL(1-15)] enhanced the antidepressant effects of FLX in naïve animals. In this work, we have analyzed in an animal model of depression, the olfactory bulbectomy (OBX) rats, the effect of GAL(1-15) on FLX-mediated responses in the forced swimming test (FST) and the sucrose preference test (SPT), tests related with despair and anhedonic behaviors. We have also studied the corticosterone levels in OBX rats after the coadministration of GAL(1-15)+FLX.

MATERIAL AND METHODS

Groups of OBX rats (n=7-9) received a subchronic pattern of FLX(10mg/Kg) alone or in combination with GAL(1-15)(1nmol) 15min before the FST or SPT.
In FST two swimming sessions were conducted: a 15min pretest followed 24h later by a 5min test. The total duration of immobility behavior, swimming and climbing were recorded during the second 5min. The administration of drugs was performed between sessions.
In SPT 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, the bottles were weighed to calculate the sucrose intake and sucrose preference.
FLX was administered sc 23, 5 and 1 hour before the test and GAL(1-15) were injected icv 15 min before the test. In the FST we also evaluated the role of GALR2 with the antagonist M871. To perform the corticosterone assay, samples from OBX animals were collected after the administration of FLX alone or in combination with GAL(1-15).
All data were analyzed using GraphPad PRISM 8.0. For comparing more than 2 groups, One-way ANOVA followed by Fisher´s least significant difference test was used.

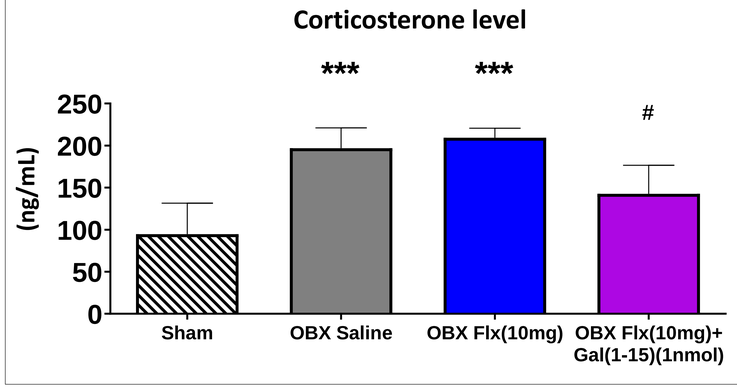
RESULTS

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 (3 nmol) blocked the GAL(1-15)-induced reduction of the immobility time.

*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); ***P <0 .001 vs rest of the groups according to one-way ANOVA followed by Fisher's least significance difference test.



Elevated corticosterone levels, characteristic of OBX animals, are not counteracted by FLX administration alone. Only the coadministration of GAL(1-15)+FLX reduced the OBX-increased corticosterone levels by around 50% compared to OBX-saline.

***P < .001 vs Sham group and #P < .05 vs rest of the groups according to one-way ANOVA followed by Fisher's least significance difference test.

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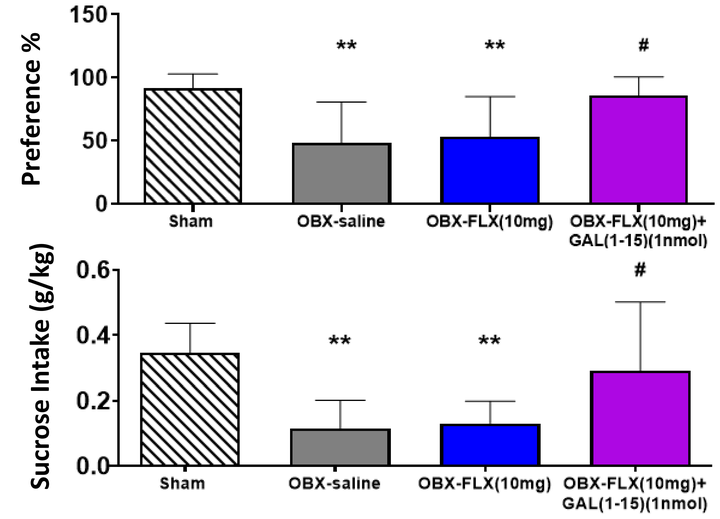
SPT



In SPT, OBX animals exhibited a reduction in sucrose intake and preference compared with sham animals. The coadministration of GAL(1-15) + FLX reversed the effects of the OBX procedure as these animals cotreated with GAL(1-15)+FLX showed a statistically significant increase in both sucrose intake compared with the OBX-saline group.

**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.

CONCLUSIONS

1. GAL(1-15) enhances the Antidepressant-Like Effects mediated by FLX in OBX rats in the FST.

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

3. The elevated corticosterone levels, characteristic of OBX animals, are only counteracted by the coadministration of GAL(1-15) and FLX. This might involve the regulatory elements of the HPA axis and opens up the possibility to use this treatment in resistant depression

4. The results open the possibility to use GAL(1-15) in combination with FLX as a novel strategy for treatment of depression.

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