

**- ABSTRACT-**

**GALANIN (1-15) ENHANCEMENT OF THE BEHAVIORAL EFFECTS OF A 5-HT<sub>1A</sub> AGONIST AND FLUOXETINE IN THE FORCED SWIMMING TEST GIVES A NEW THERAPEUTIC STRATEGY AGAINST DEPRESSION: POSSIBLE ROLE OF GALR1-GALR2-5-HT<sub>1A</sub> HETERORECEPTOR COMPLEXES**

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Major Depression is the most frequent mood disorder, with a lifetime prevalence that has been reported to range from 7% to 21%. It is associated with a substantial functional impairment, diminished quality of life, increased burden both for patients and caregivers, as well as with a higher risk of mortality.

Although the underlying mechanisms have not yet been clearly defined in the last decade the importance of the role of neuropeptides, including Galanin (GAL) and the N-terminal fragment GAL(1-15) and/or their receptors in the treatment of stress-related mood disorders is becoming increasingly apparent.

We have described that GAL(1-15) induces strong depression-related and anxiogenic-like effects in rats and these effects were significantly stronger than the ones induced by GAL. The GALR1-GALR2 heteroreceptor complexes in the dorsal hippocampus and dorsal raphe (DR) were involved in these effects and demonstrated also in cellular models.

Although several neurotransmitter systems and brain areas have been implicated in depression, the pharmacological treatment of major depression is mainly based on drugs elevating serotonergic (5-HT) activity. Specifically,

selective 5-HT reuptake inhibitors (SRRIs) are the most commonly used for treatment of major depression. In particular, Fluoxetine (FLX) is usually chosen for the treatment of symptoms of depression

In view of these results the purpose of the current study was to assess the ability of GAL(1–15) to modulate the behavioral effects of the 5-HT<sub>1A</sub> agonist 8-OH-DPAT and FLX.

We have analyzed the effect of GAL (1–15) on the 5-HT<sub>1A</sub> agonist 8-OH-DPAT and FLX-mediated responses in a behavioral test of depression. We tested the involvement of GALR using an *in vivo* of siRNA GALR1 or siRNA GALR2 knockdown rats. Moreover, to study whether the effects of GAL(1–15) on FLX action were mediated via 5-HT<sub>1A</sub>, we have analyzed the effect of the 5-HT<sub>1A</sub> antagonist WAY100635 in the GAL(1-15)-mediated effect in the FST. We have also determined the binding characteristics and mRNA levels of 5-HT<sub>1A</sub> in the DR and dorsal hippocampus after GAL(1-15)-FLX administration.

GAL(1-15) enhances the antidepressant-like effects induced by the 5-HT<sub>1A</sub> agonist 8-OH-DPAT or FLX in the forced swimming test (FST), and we demonstrate the involvement of GALR1/GALR2 heteroreceptor complex in the GAL(1-15)-mediated effect using *in vivo* rat models for siRNA GALR1 or GALR2 knockdown. The results on the proximity ligation assay (PLA) suggest the existence of GALR1-GALR2-5-HT<sub>1A</sub> heteroreceptor complexes since positive PLA were obtained for both GALR1-5-HT<sub>1A</sub> and GALR2-5-HT<sub>1A</sub> complexes in the DR and hippocampus.

Importantly, 5-HT<sub>1A</sub> receptors (5HT<sub>1A</sub>R) also participate in the GAL(1-15)/FLX interactions since the 5HT<sub>1A</sub>R antagonist WAY100635 blocked the behavioral effects in the FST induced by the coadministration of GAL(1-15) and FLX. The mechanism underlying GAL(1-15)/FLX interactions affected the binding characteristics as well as the mRNA levels of 5-HT<sub>1A</sub>R specifically in the dorsal hippocampus.

The results open up the possibility to use GAL(1-15) as for a combination therapy with FLX for treatment of depression and to develop novel drugs

specifically targeting GALR1-GALR2-5-HT1AR heteroreceptor complexes  
complexes as a novel strategy for treatment of depression.