GALANIN (1-15) ENHANCES THE BEHAVIORAL EFFECTS OF FLUOXETINE IN THE FORCED SWIMMING TEST: A NEW THERAPEUTIC STRATEGY AGAINST DEPRESSION

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The selective serotonergic (5- HT) reuptake inhibitors, including Fluoxetine (FLX), are the most commonly used for treatment of major depression. However, the understanding of the mechanism of action of FLX beyond its effect of elevating 5-HT is limited. The interaction between 5-HT system and neuropeptides signaling could be a key aspect. The neuropeptide Galanin(1-15) [GAL(1-15)], induced a strong depression-like and anxiogenic-like effects in the forced swimming test (FST), the tail suspension test, the open field and the light/dark test. The GALR1-GALR2 heteroreceptor complexes in the dorsal hippocampus and in the dorsal raphe were involved in these effects.

We have analyzed the effect of GAL(1–15) on FLX-mediated responses in the FST. We tested the involvement of GALR in the GAL(1–15) effect with the selective GALR2 antagonist M871 and using siRNA GALR2 or GALR1 knockdown rats.

Groups of rats received three injections of sc FLX(2.5mg/Kg) or FLX(10mg/Kg) and a single icv injection of a threshold dose of GAL(1-15)(1nmol) 15 minutes before the FST. In a second set of experiments, we determined the involvement of GALR1 and GALR2 in the effect of GAL(1-15) on FLX-mediated action. Groups of rats received three injections of sc FLX(10mg/kg), a single icv injection of GAL(1-15) (1nmol) and the GALR2 antagonist M871 (3nmol) icv alone or in combination. Also, in siRNA GALR1 or GALR2 knockdown rats we coadministered FLX(10mg/Kg) and GAL(1-15)(1nmol).

The coadministration of sc FLX(2.5mg/Kg) and icv injection of GAL(1-15)(1nmol) induced antidepressant-like effects with a significant decrease in the immobility ($p<0.05$). Moreover, an increase in the swimming time ($p <0.05$) was also observed.
The strong enhancement by GAL(1-15) of the antidepressant-like effects mediated by FLX was validated using the effective dose of FLX 10mg/kg. Icv GAL(1-15) significantly decreased the immobility time induced by the effective dose of FLX(10mg/kg) by 50% in the FST ($p<0.05$). Moreover, an increase of the swimming time by about 40% versus FLX(10mg/kg) group was also observed ($p<0.01$).

The GALR2 antagonist M871 3nmol significantly blocked the GAL(1–15)-induced reduction of the immobility time ($p<0.05$), and increase in the swimming time ($p<0.01$) found after coadministration of icv injection of GAL(1-15) and sc FLX(10mg/kg) in the FST.

The coadministration of sc FLX(10mg/kg) and icv injection of GAL(1-15) in siRNA GALR1 or GALR2 knockdown animals did not produce a further reduction of the immobility time and a further increase in the swimming time compared to FLX alone.

In the current study we describe for the first time that GAL(1-15) enhances the antidepressant-like effects induced by FLX in the FST. Indications were also obtained for the involvement of a GALR1/GALR2 heteroreceptor complex in the GAL (1-15)-mediated actions based on the use of the specific GALR2 antagonist M871 and icv injections of GALR1 siRNA or GALR2 siRNA producing a reduction of GALR1 or GALR2, respectively**.** The results open up the possibility to use GAL(1-15) as for a combination therapy with FLX as a novel strategy for treatment of depression.

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