

THE 5-HT_{1A} RECEPTORS ARE INVOLVED IN THE EFFECT OF GALANIN(1-15) ON FLUOXETINE-MEDIATED ACTION IN THE FORCED SWIMMING TEST

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We have described that Galanin N-terminal fragment (1-15) [GAL(1-15)] is associated with depressive effects and also modulates the antidepressant effects induced by the 5-HT_{1A} receptor (5-HT_{1AR}) agonist 8-OH-DPAT in the forced swimming test (FST). Importantly, the mechanism underlying this action involved interactions at the receptor level in the plasma membrane with changes also at the transcriptional level. Thus, GAL(1-15) affected the binding characteristics as well as the mRNA levels of 5-HT_{1AR} in the dorsal hippocampus and dorsal raphe (DR).

Recently, we observed that GAL(1-15) enhanced the antidepressant-like effects induced by Fluoxetine (FLX) in the FST. In view of this, we have studied whether the effects of GAL(1-15) on FLX action were mediated via 5-HT_{1AR}, analyzing the effect of the 5-HT_{1AR} 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_{1AR} in the DR and dorsal hippocampus after GAL(1-15)-FLX administration.

To study if the effects of GAL(1-15) on FLX action were mediated via the 5HT_{1AR}, groups of rats (n=6-8 rats per groups) received three subcutaneous injections (sc) of FLX(10mg/kg) and 15 minutes before the FST a single intracerebroventricular injection (icv) of GAL(1-15) (1nmol) and 5HT_{1AR} antagonist WAY100635(6nmol) icv alone or in combination.

In the second set of experiments, we analyzed the effects of the three injections of sc FLX or Vehicle and a single icv injection of GAL(1-15) or aCSF and sacrificed 30 min later to analyze the binding characteristics of the 5-HT_{1AR} agonist [³H]-8-OH-DPAT and 5-HT_{1A} mRNA levels in sections of the DR and Dorsal Hippocampus, specifically in the Ammon's horn 1 (CA1) and Dentate Gyrus (DG).

The results confirmed that the 5HT_{1AR} participates in this interaction as the 5HT_{1AR} antagonist WAY100635 (6nmol) significantly blocked the reduction in immobility time (p<0.05), and the increase in swimming time (p<0.01) induced by the coadministration of icv GAL(1-15) and the three injections of sc FLX(10mg/kg) in the FST.

The coadministration of the three sc injections of FLX(10mg/Kg) and a single icv injection of GAL(1-15)(1nmol) produced a significant increase in the 5HT_{1AR} mRNA levels in CA1 (p<0.05) and DG (p<0.05) of the dorsal hippocampus compared to controls and single treatments. This effect was not observed in the DR.

In the autoradiographic experiments, the coadministration of the three injections of sc FLX(10mg/Kg) and a single icv injection of GAL(1-15)(1nmol) produced a significant decrease in the K_d value (p<0.01) and in the B_{max} value (p<0.05) of the agonist radioligand [³H]-8-OH-DPAT in the DG of the dorsal Hippocampus compared to FLX(10mg/Kg) alone.

These effects were not observed in the CA1 area of the Hippocampus or in the DR. These results indicate that 5HT1AR participates in the GAL(1-15)/FLX interactions in the FST. The mechanism underlying GAL(1-15)/FLX interactions affected the binding characteristics as well as the mRNA levels of 5-HT1AR specifically in the dorsal hippocampus while leaving unaffected mRNA levels and affinity and binding sites of this receptor in the DR. The target for GAL(1-15) may mainly be 5-HT1AR-GALR1-GALR2 heteroreceptor complexes located postjunctionally in the dorsal hippocampus.

This work was supported by Spanish grants SAF2016-79008-P; PSI2013-44901-P.

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