- ABSTRACT-

GALANIN AND GALANIN FRAGMENT 1-15 MODULATE ANTIDEPRESSANT RESPONSES BY TARGETING 5-HT1AR-GALR HETERORECEPTOR COMPLEXES OF THE ASCENDING MIDBRAIN SEROTONIN PATHWAYS

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Mood disorders, including depression and anxiety, are among the most prevalent mental illnesses with high socioeconomic impact. 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/or their receptors in the treatment of stress-related mood disorders is becoming increasingly apparent.

GAL is involved in mood regulation, including depression-related and anxiety-like behaviors. Activation of GALR1 and GALR3 receptors results in a depression like behavior while stimulation of GALR2 receptor leads to anti-depressant-like effects. Moreover, GAL modulates 5-HT1A receptors (5-HT1AR), a key receptor in depression at autoreceptor and postsynaptic level in the brain. This interaction can in part be due to the existence of GALR1-5-HT1AR heteroreceptor complexes in discrete brain regions [1]. Not only GAL but also the N-terminal fragments like GAL(1-15) are active in the Central Nervous System [2, 3]. Recently, we 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 [4]. The GALR1-GALR2

heteroreceptor complexes in the dorsal hippocampus and especially in the dorsal raphe (DR), areas rich in GAL(1-15) binding sites [5] were involved in these effects [4, 6] and demonstrated also in cellular models.

In the present study, we have analyzed the ability of GAL(1-15) to modulate 5-HT1AR located at postjunctional sites and at the soma-dendritic level in rats. We have analyzed the effect of GAL(1-15) on the 5-HT1AR-mediated response in a behavioral test of depression and the involvement of the GALR2 in these effects. GAL(1-15) enhanced the antidepressant effects induced by the 5-HT1AR agonist 8-OH-DPAT in the forced swimming test [7]. These effects were stronger than the ones induced by GAL. The mechanism of 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 level of 5-HT1AR in the dorsal hippocampus and DR. GALR2 was involved in these effects, since the specific GALR2 antagonist M871 blocked GAL(1-15) mediated actions at the behavioral and receptor level [7].

Furthermore, the results on the proximity ligation assay (PLA) in this work suggest the existence of GALR1-GALR2-5-HT1AR heteroreceptor complexes since positive PLA were obtained for both GALR1-5-HT1AR and GALR2-5-HT1AR complexes in the DR and hippocampus. Moreover the studies on RN33B cells, where GALR1, GALR2 and 5-HT1AR exist [4], also showed PLA-positive clusters indicating the existence of GALR1-5-HT1AR and GALR2-5-HT1AR complexes in these cells [7].

In conclusion, our results indicate that GAL(1–15) enhances the antidepressant effects induced by the 5-HT1AR agonist 8-OH-DPAT probably acting on GALR1-GALR2-5-HT1AR heteroreceptor located at postjunctional sites and at the soma-dendritic level. The development of new drugs specifically targeting these heteroreceptor complexes may offer a novel strategy for treatment of depression.

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