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 antidepressant-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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1. Borroto-Escuela, D.O., et al., Galanin receptor-1 modulates 5-
hydroxytryptamine-1A signaling via heterodimerization. Biochem Biophys Res


