The effect of galanin n-terminal fragment (1–15) in anhedonia: involvement of the dopaminergic mesolimbic system.

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Abstract:
The Galanin N-terminal fragment (1–15) [GAL(1–15)] induces depressant– and anxiogenic–like actions in behavioral tests and these effects were significantly stronger than the ones induced by Galanin. Since anhedonia is a core feature of depression, we have analyzed GAL(1–15) actions in two anhedonic–like behavior tests: saccharin Self-administration and Sucrose Preference test (SPT). In order to investigate whether the effect of GAL(1–15) was associated with the reward circuit, we have studied the GAL(1–15) actions over the mesolimbic system by the expression of the C–Fos, Dat, Vmat2 and Dopamine and GAL receptors genes in VTA and NAc. Three sets of experiments were conducted in the saccharin Self-administration test. In the first, a dose–response curve of GAL(1–15) 1nmol, 3nmol or vehicle was performed. We have also compared the effects in the number of saccharine reinforcements of GAL 3nmol and GAL(1–15) 3nmol. In the last experiments, rats received i.c.v. GAL(1–15) 3nmol and the GALR2 antagonist M871 3nmol. In SPT, we have analyzed the effects of GAL(1–15) 3nmol in the sucrose intake and preference after 2, 8 and 24 h. In the qPCR experiments, groups of rats were killed 1h after i.c.v. GAL(1–15) 3nmol or vehicle. The VTA and NAc were dissected and the mRNA expression of C–Fos, Dat, Vmat2 and D1, D2, D3, D5, GALR1, and GALR2 receptors were measured. GAL(1–15) 3nmol significantly decreased the number of reinforcement of saccharin self–administer (p<0.01), while 1nmol lacked effect. GAL(1–15) also significantly reduced the number of reinforcement (p<0.01)
compared with GAL. The GALR2 antagonist M871 significantly blocked (p<0.05) the decrease in the number of saccharin reinforcements induced by GAL(1−15). In the SPT, GAL(1−15) decreased the sucrose intake 8 (p<0.05) and 24 hours (p<0.01) after administration. GAL(1−15) at a dose of 3 nmol produced a significant decrease in the mRNA levels of Dat and Vmat2 (p<0.05) and an increase in the D3 receptor (p<0.05) in VTA. In the NAc, GAL(1−15) induced a significant decrease in the expression of C−Fos (p<0.05) mRNA and a significantly increased the mRNA expression of D1 (p<0.05), D2 (p<0.05) and D3 (p<0.05). In the current study, we described for the first time that GAL(1−15) induced a strong anhedonia−like phenotype in several behavioral tests, confirming an important role of this neuropeptide in anhedonia, moreover, the dopaminergic mesolimbic system was described as a key region in GAL(1−15)−mediated action on anhedonia. These results may give the basis for the development of novel therapeutic strategies using GAL(1−15) for treatment of depression and reward−related diseases.

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