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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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