Galanin N-terminal fragment (1-15) reduces alcohol consumption in the self-administration with involvement of mesocorticolimbic system in rats

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INTRODUCTION

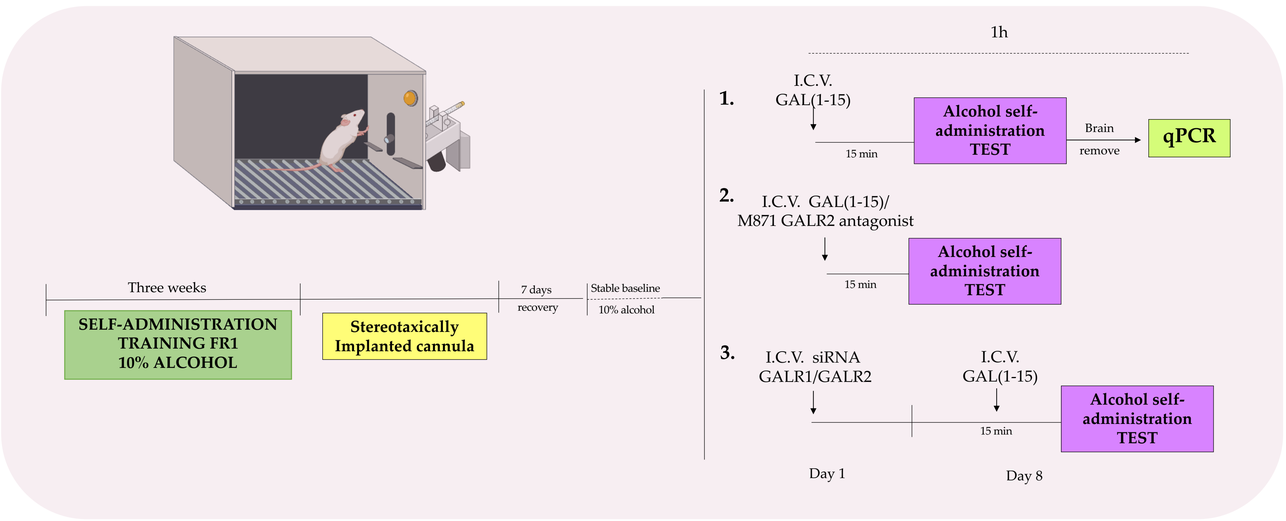
Alcohol Use Disorder (AUD) is a highly prevalent disorder characterized by an **impaired ability to stop/control alcohol use despite the adverse consequences.** However, pharmacotherapies have **seen limited use in the treatment of AUD, partially due to the low efficacy of the medication**. Therefore, it is **essential to find new biological targets that could modulate alcohol consumption**. Our research group discovered that the **fragment of Galanin 1-15 [GAL(1-15)] a neuropeptide widely distributed in the central nervous system, induces a substantial reduction in preference and voluntary alcohol consumption in rats**. To investigate the role of GAL(1-15) in alcohol **seeking-behaviour, we used the self-administration in rats. Moreover, GALR1 and GALR2 in GAL(1-15)-mediated effects in this test were analyzed with the selective GALR2 antagonist M871 and using an in vivo model siRNA GALR1 or GALR2 knockdown rats. Also, we analyzed the mesocorticolimbic system on the mRNA expression.**

MATERIAL AND METHODS

Three sets of experiments were conducted on the alcohol self-administration:

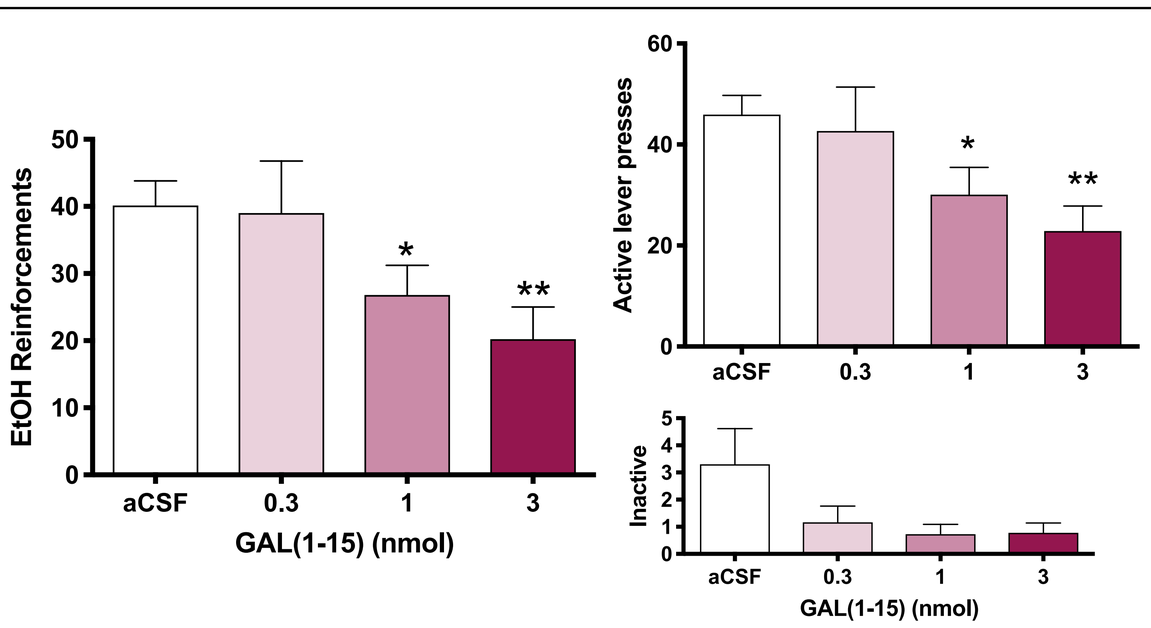
- **1. A dose-response curve of GAL(1-15) was performed**. For this, groups of rats received icv GAL (1-15) 0.3, 1 and 3 nmol or cerebrospinal fluid-injected (aCSF) 15 min before the test. Rats from the alcohol self-administration test were euthanised by decapitation 1 h after a single icv administration of GAL (1-15) 3 nmol or aCSF.**We analyzed mRNA expression of C-Fos** in the ventral tegmental area (VTA), accumbens nucleus (NAc) and prefrontal cortex (PFC).
- **2. The GAL receptors involved in the effect of GAL(1-15) were studied**; for this, groups of rats received icv GAL (1-15) 3 nmol, M871 3nmol antagonist, GAL(1-15) 3nmol combined with GALR2 antagonist or aCSF 15 min before the test.
- **3. We have used knockdown rats for Galanin receptors GALR1 or GALR2 in the alcohol self-administration test.** siRNA GALR1, siRNA GALR2 or Delivery Media (DM) were injected icv eight days before the alcohol self-administration test. GAL(1-15) or aCSF were injected 15 min before the test.
- One-way ANOVA followed by Fisher's least significant difference test was used

Male Sprague-Dawley rats were trained to self-administer 10% alcohol under fixed-ratio FR1 in the self-administration boxes.



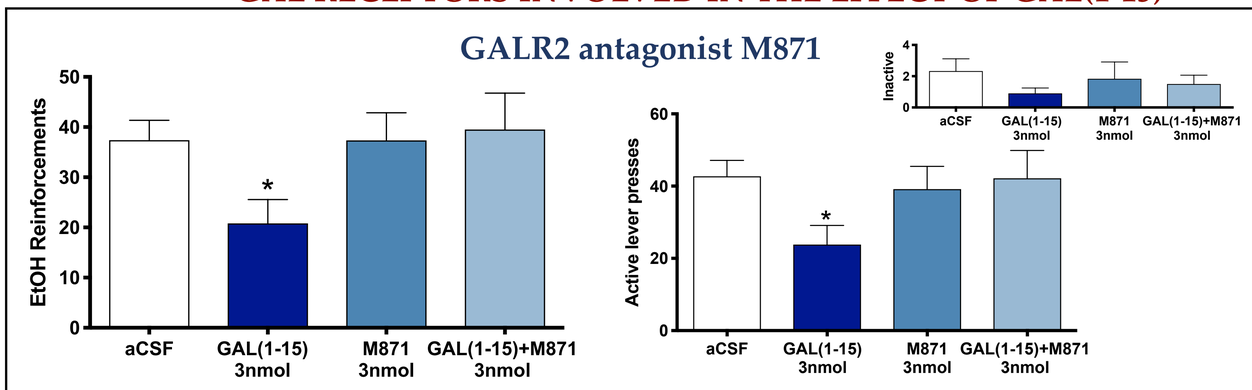
RESULTS

DOSE-RESPONSE CURVE OF GAL(1-15)

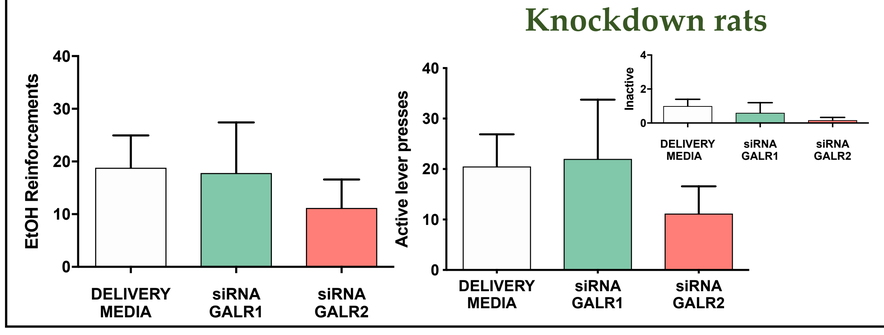


GAL(1-15) 3 nmol induced a significant reduction in the number of reinforcements by 50% and in the active lever presses by 48% compared with control animals. GAL(1-15)1 nmol induced a less strong but significant reduction in this parameters ($p<0.05$). **GAL(1-15) 0.3 nmol lacked an effect** in the alcohol self-administration.

GAL RECEPTORS INVOLVED IN THE EFFECT OF GAL(1-15)

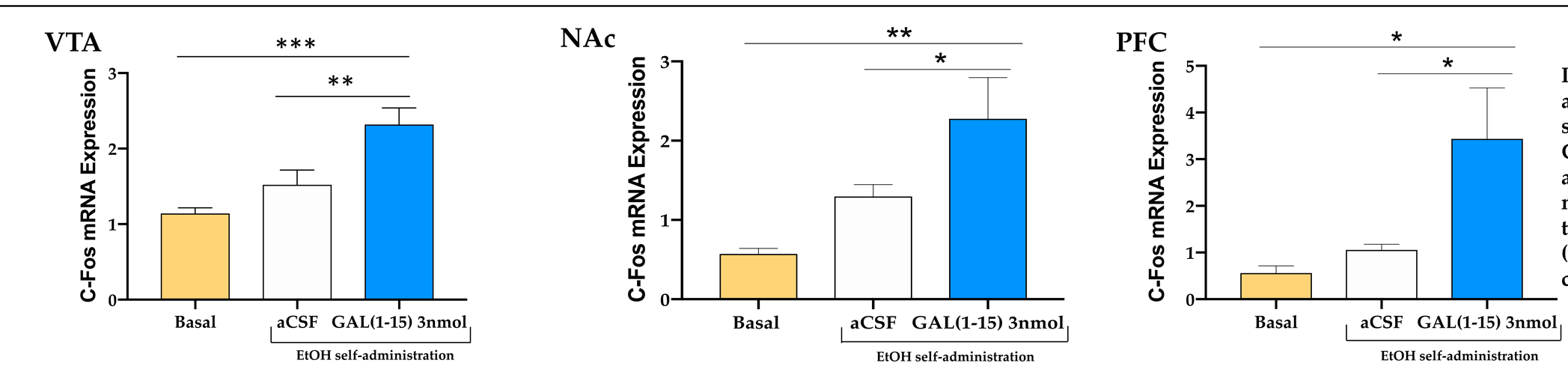


M871 significantly blocked the GAL(1-15) induced reduction in the nº of reinforcements and in the nº of active lever presses



Downregulation of GALR1 or GALR2 by siRNA did not affect any parameter in the alcohol self-administration. The decrease in siRNA GALR1 and siRNA GALR2 was sufficient to block the effect of GAL(1-15).

mRNA EXPRESSION OF C-FOS



In animals under chronic alcohol consumption by self-administration, GAL(1-15) 3 nmol produced a significant increase in the mRNA levels of C-Fos in the VTA ($P<0.01$), NAc ($p<0.05$) and PFC ($p<0.05$) compared with aCSF group.

CONCLUSION

- **GAL(1-15) strongly reduced alcohol-seeking behaviour in the operant model of alcohol self-administration.**
- **GALR1 and GALR2 were involved in these effects:** GALR2 antagonist M871 blocked the GAL(1-15) mediated action in alcohol self-administration, and the downregulation of GALR1 and GALR2 by siRNA was sufficient to block the GAL(1-15) effect.
- **The mesocorticolimbic circuitry participates in the mechanism of GAL(1-15) behaviour-mediated actions** since we observed changes in the immediate-early gene C-Fos, in the VTA, NAc and PFC.
- **These results open up the possibility of using GAL(1-15) as a novel strategy in AUD.**

SCAN ME

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