Efficacy of the intranasal route for the administration of NPY1R and its effects on the treatment of neurodegenerative and mood disorders via heteroreceptor complexes formation

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Introduction

Dysregulation of adult hippocampal neurogenesis has been implicated in currently highly prevalent neuropsychiatric disorders such as major depressive disorder (MDD) or cognitive decline such as Alzheimer's disease (AD). The neuropeptide Y1 receptor (Y1R) of neuropeptide Y (NPY) has been found to interact with galanin receptor 2 (GALR2) in certain areas of the hippocampus with effects on memory processes and mood-related behaviour within 24 hours of intranasal administration. This study addresses the synergistic effects of the long-term NPY1R-GALR2 interaction on both mood-related behaviour and cognitive function following intranasal co-administration, as well as exploring other interactions of NPY1R. These changes have been assessed at molecular, cellular and behavioural levels.

Method

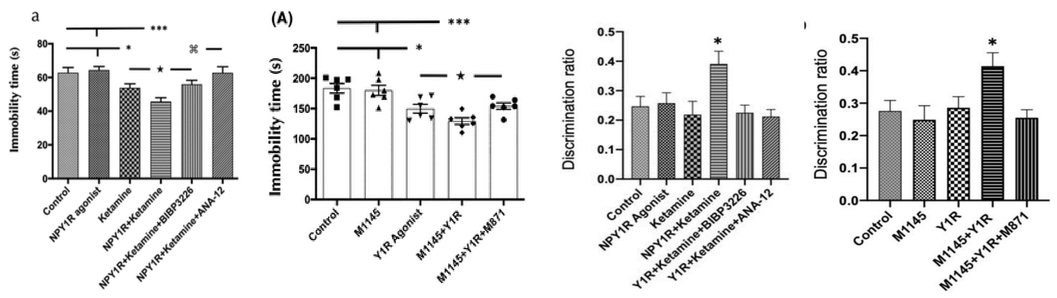
GALR2 and/or NPY1R agonists were administered intranasally, while other cohort of rats received ketamine and/or NPY1R agonist. Behaviour was assessed using the Forced Swimming Test (FST) to analyse antidepressant activity and the object-in-place task for spatial memory. In brain slices, we performed in situ PLA techniques to detect GALR2-NPYY1R and NPY1R-TrkB heteroreceptor complexes formation, as well as different immunolabelling techniques with proliferating cell nuclear antigen (PCNA), doublecortin (DCX), bromodeoxyuridine (BrdU) and brain-derived neurotrophic factor (BDNF).

Results

The results show that the interaction of NPYY1R with both GALR2 and TrkB enhances antidepressant behaviour and spatial memory, while increasing the formation of heteroreceptor complexes (GALR2-NPYY1R or NPY1R-TrkB) in the dentate gyrus of the hippocampus. Both treatments promote neuroblast proliferation, survival as well as neuronal differentiation and maturation. In addition, co-stimulation of NPY1R-TrkB enhances BDNF expression.

Behavioural outcomes

Following intranasal co-administration of a NPYY1R agonist with ketamine or a NPYY1R agonist with GALR2 , a decrease in immobility behaviour in the forced swimming (1) and test an increase in the discrimination coefficient in the object-in-place task (2) have been observed in a physiological rat model. Furthermore, this result correlates with an increase in the number of NPY1R-TrKb or NPY1R- GALR2 heteroreceptor complex formation in the hippocampus.

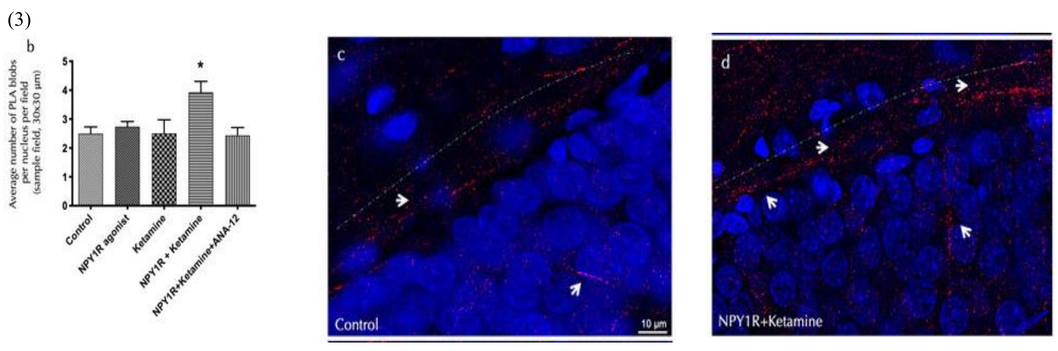


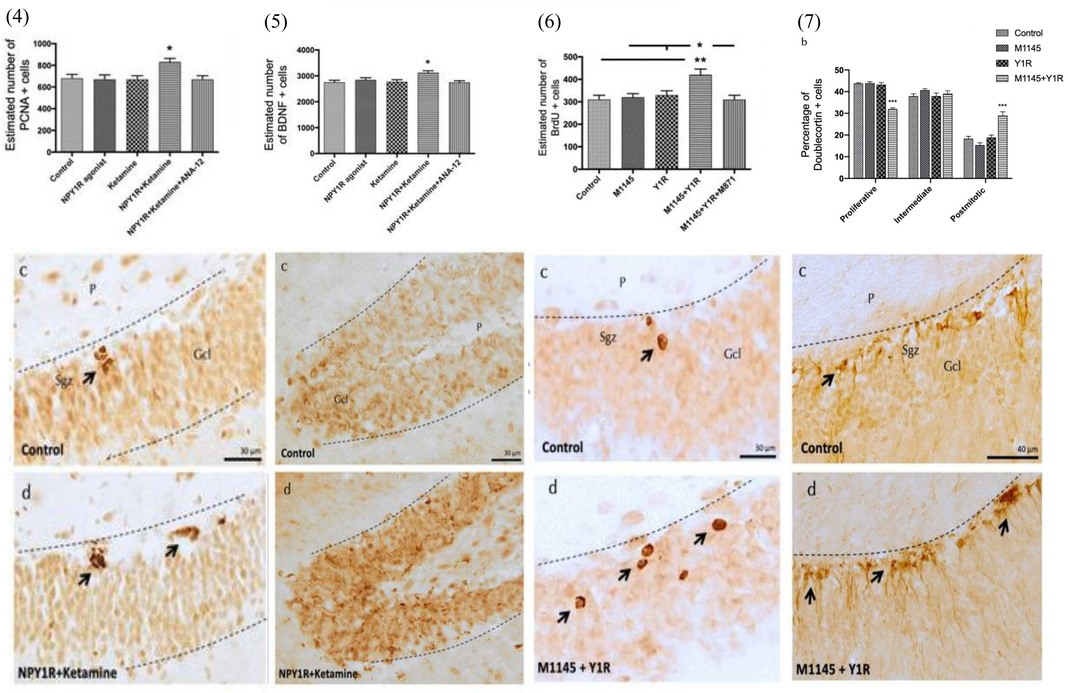
Immunohistochemistry and in situ Proximity Ligation Assay

Dorsal Hippocampus

On dorsal hippocampus, PLA shows an increase in the formation of NPY1R-TrKb heteroreceptor complexes (3) after the coadministration of its agonists, and it seems to be related to the improvement of the spatial memory and the increase in the number of PCNA (4) and BDNF (5) immunolabelled cells. On the other hand, NPY1R-GALR2 interaction seems to increase the number of Brdu + cells (6) as well as enhance the expression of doublecortin and the differentiation of doublecortin +cells (7).

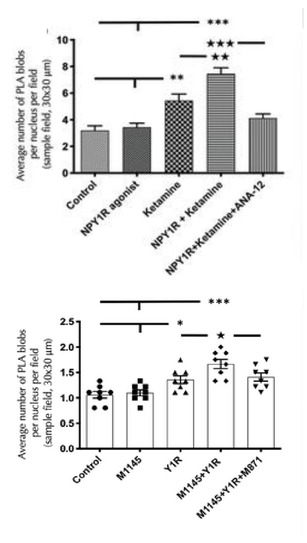
(3)

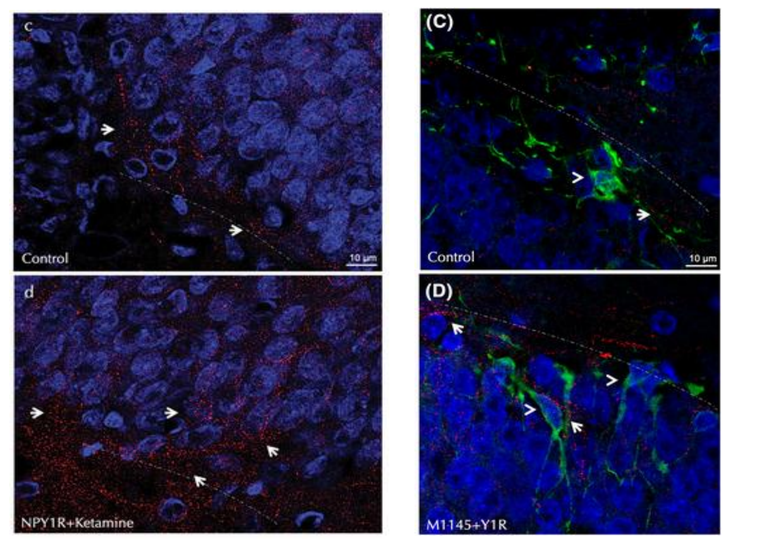


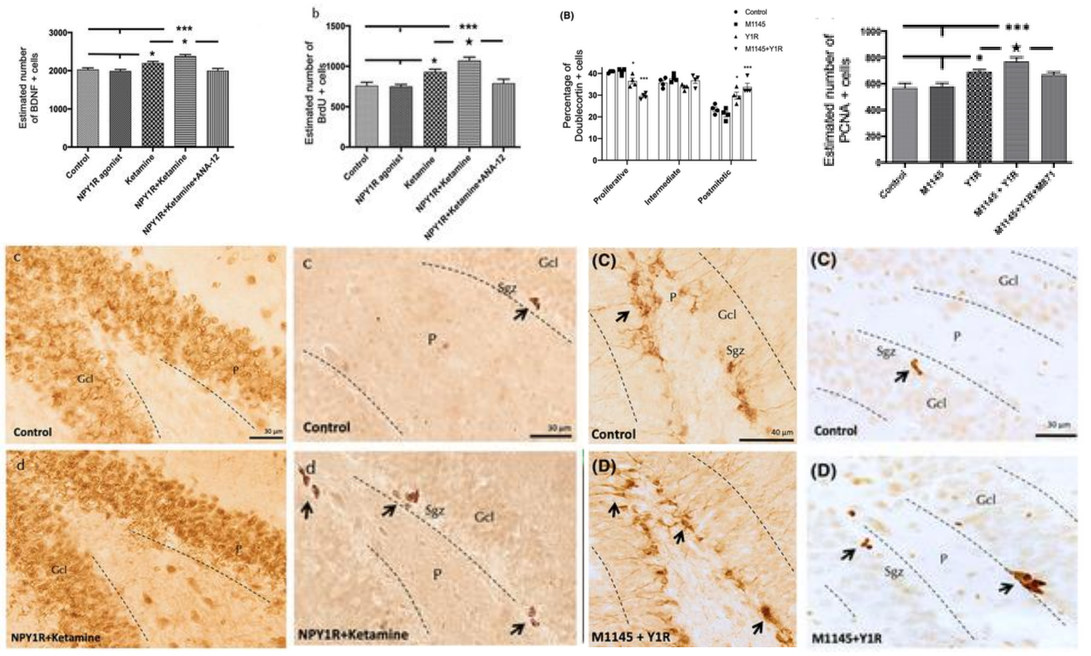


Ventral Hippocampus

In situ PLA of NPY1R-Trkb (8) and NPY1R-GALR2 (9) reveals an increase in the formation of these kind of heteroreceptor complexes after coadministration of their respective agonists as same as increase the antidepressant-behaviour in rats. Specifically, , NPY1R-GALR2 heterorreceptor complexes has seen to be more related to an enhanced in the BDNF + cells (10) in the hippocampus at the same time as BRDU cells (11) are remarkably higher after coadministration. On the other hand, NPY1R-Trkb has reveal an increse in the formation an differentiation of doublecortin +cells (12), which are precisely the cells that express more frequently these heteroreceptor complexes. Also, PCNA immunostaining cells (13) reveals an augmented number of these after coadministration of both treatments.







Conclusion

Our results contribute to the understanding of neuroplasticity mediated by the formation of NPY1R-GALR2 and NPY1R-TrkB heteroreceptor complexes following intranasal administration of NPY1R and GALR2 agonists, highlighting their role in enhancing the processes of neurogenesis, neuronal survival and maturation. These findings open up new therapeutic approaches for the treatment of MDD and AD.

More information

NPYY1R- GALR2

NPYY1R-TRKB

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