Positive allosteric modulation of metabotropic glutamate 5 receptors prevents and reverses social discrimination deficits in rats

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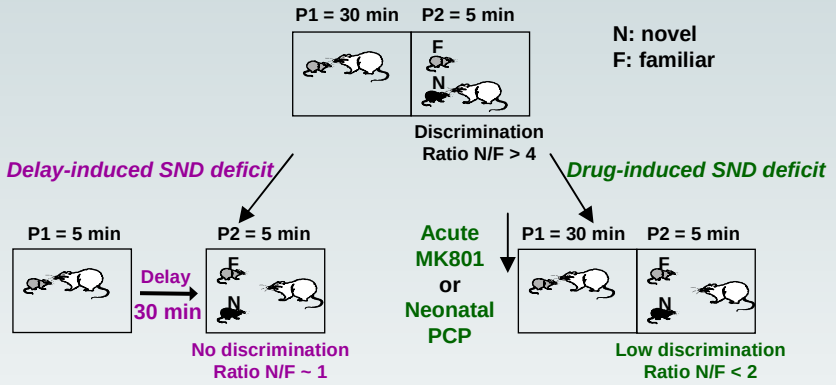
INTRODUCTION

Altered glutamatergic transmission is involved in the pathophysiology of schizophrenia, and restoration of deficient N-methyl-D-aspartate (NMDA) receptor hypoactivity is considered as a therapeutic strategy [1]. Recently, metabotropic glutamatergic (mGlu) receptors have been identified as targets for psychiatric disorders. Indeed, agents that stimulate mGlu5 receptors can improve NMDA transmission [2].

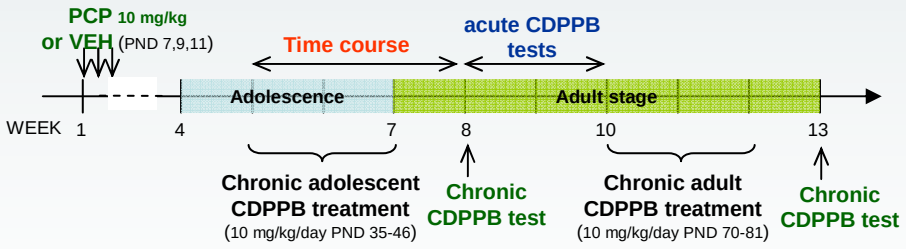
The social novelty discrimination (SND) test [3] is used to assess cognitive function related to cognitive symptoms in schizophrenia. We purpose to evaluate the action of a positive mGlu5 receptor allosteric modulator, CDPPB, on delay- , dizocilpin (MK801)- and neonatal PCP-induced SND deficit, a developmental model of schizophrenia. We also examine the age-specific expression of neonatal PCP-induced deficit in SND. Then, chronic CDPPB treatment was used to target different developmental periods in neonatal PCP-treated rats.

METHODS

Social Novelty Discrimination Paradigm

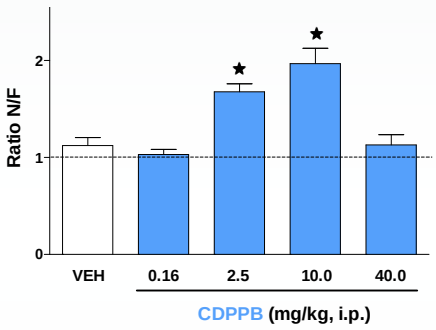


Test procedure of the neonatal PCP model

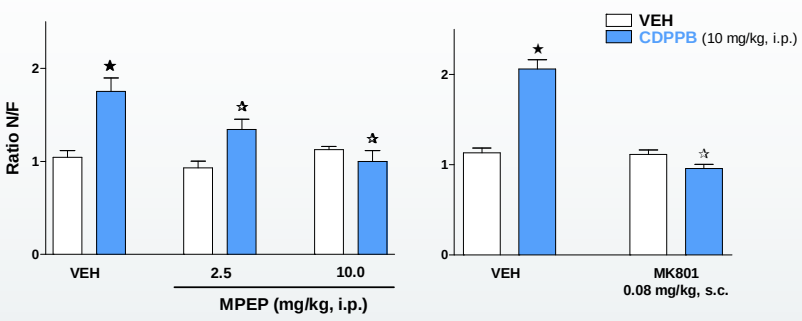


DELAY-INDUCED SND DEFICIT

CDPPB improves novelty discrimination

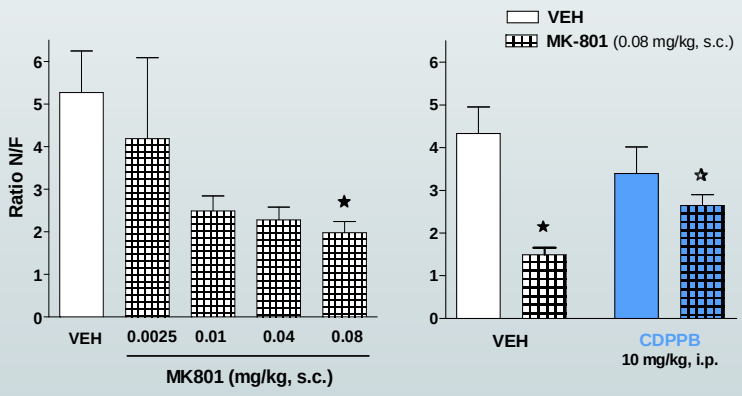


The beneficial effect of CDPPB is blocked by MPEP and MK801



MK801-INDUCED SND DEFICIT

CDPPB attenuates the deficit of SND induced by MK801



Acknowledgements and References

Chronic CDPPB experiments were executed by N.E. Clifton and time-course experiments by F. Loiseau.

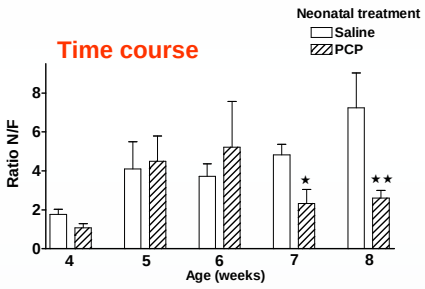
[1] Javitt, D. C., 2010. Isr J Psychiatry Relat Sci 47, 4-16.

[2] Kanuma, K., Aoki, T., Shimazaki, Y., 2010. Recent Pat CNS Drug Discov 5, 23-34.

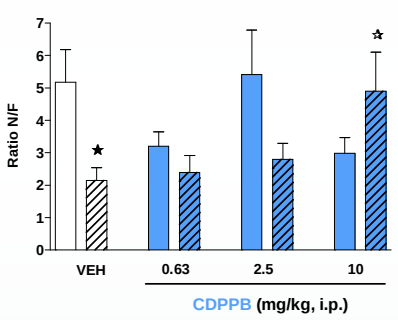
[3] Harich, S., Gross, G., and Bespalov, A., 2007. Psychopharmacology (Berl.) 192, 511-519.

NEONATAL PCP-INDUCED SND DEFICIT

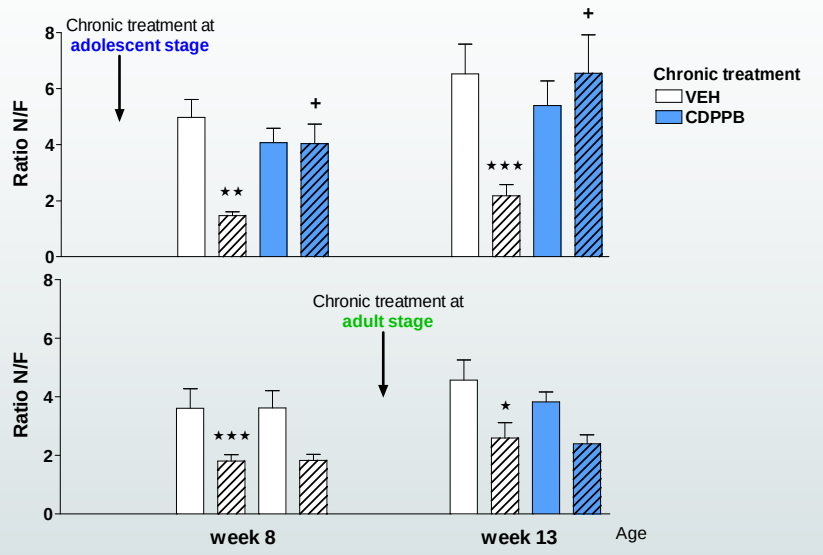
Neonatal PCP-induced SND deficit appears at adult stage



Acute CDPPB reverses the neonatal PCP-induced SND deficit



Adolescent but not adult chronic CDPPB treatment prevents the neonatal PCP-induced SND deficit



CONCLUSION

The beneficial effect of CDPPB on social cognition is specific of mGlu5 receptor modulation and functionally related to NMDA receptors activity.

The neonatal PCP-induced SND deficit emerges at a developmental period that corresponds to young adulthood in the human, demonstrating an important similarity to real schizophrenia progression. CDPPB not only reverses, but also prevents, SND deficits associated with a developmental model of schizophrenia.

These findings point to the modulation of mGlu5 receptor as potential target for reducing cognitive impairment associated with psychatric disorders.