P.269 THE AMPAKINE CX717 HAS A RAPID, BUT SHORT-LASTING ANTIDEPRESSANT-LIKE ACTIVITY IN THE RAT

Marta Gordillo-Salas¹, Jun Ren², John Greer² & Albert Adell^{1,3}

¹ Institute of Biomedicine & Biotechnology of Cantabria, IBBTEC (CSIC-UC), Santander, Spain.

² University of Alberta, Department of Physiology, Edmonton, Canada.

³ CIBERSAM, Biomedical Research Networking Center Consortium, Mental Health, Santander, Spain.

INTRODUCTION

Major depressive disorder (MDD) is the most prevalent of psychiatric disorders. Currently available antidepressant drugs increase the availability of certain neurotransmitters in the brain. Briefly, it has been proposed that increasing the activity of serotonin, noradrenaline and dopamine might help lessen depression and anxiety. However, these medications can take up to several weeks to be effective. In recent years, new approaches have emerged to treat MDD. Among them, ketamine, scopolamine and deep brain stimulation (DBS) have exhibited fast and sustained therapeutic action. Interestingly, these novel therapies require the stimulation of AMPA glutamate receptors to exert their antidepressant effects. Consequently, it has been proposed that ampakines may be associated with mood enhancing properties.

AIM OF THE STUDY

The aim of the present work was to investigate the antidepressant-like effects of the ampakine CX717 in the forced swim test (FST), which is one of the most commonly used assays for the study of depressive-like behavior in rodents. The changes in intracellular signaling pathways and cortical transmitter release over time were also examined.

METHODS

Animals: Male Sprague-Dawley rats (Envigo) weighing 280–350g.

Drug administration: CX717 (20 mg/kg) was dissolved in 33% 2-hydroxypropyl-β-cyclodextrine (HPCD, Sigma-Aldrich) and injected IP. This solution was further diluted to 300 μM in artificial CSF for intracortical infusion through dialysis probes implanted bilaterally in the medial prefrontal cortex (mPFC; AP: +3.2, ML: ±0.5 and DV: -5.4).

Forced swimming test (FST): Immobility, climbing and swimming were measured.

In vivo microdialysis: Extracellular levels of serotonin (5-HT), noradrenaline (NA), dopamine (DA) and glutamate (Glu) were determined using an Alexys® Analyzer (Antec, The Netherlands).

Western blotting: After the administration of 20 mg/kg of CX717, animals were killed by decapitation, their brains removed from the skulls, and mPFCs dissected out on ice and rapidly stored at -80 °C. The sources and dilution of primary antibodies used were: rabbit anti-BDNF (1:250), rabbit anti-GluA1 (1:700), mouse anti-GFAP (1:1000), rabbit anti-EAAT1 (1:500).

Statistical analysis: Student t-test or two-way ANOVA followed by Newman-Keuls *post-hoc* test. Data expressed as mean ± SEM.

RESULTS

The administration of 20 mg/kg CX717 elicits antidepressant-like effects (measured as reduction of immobility) that last up to 24 h (Test +1), but not seven days (Test +7) later. *P < 0.05, two-tailed Student's t-test.

The administration of 20 mg/kg CX717 does not alter extracellular concentrations of monoamines and glutamate.

The local infusion of 300 μM CX717 bilaterally in the mPFC (black bar) increases the extracellular concentration of monoamines without altering that of glutamate. *P < 0.05, Newman-Keul's test after significant repeated measures ANOVA.

The intraperitoneal administration of 20 mg/kg CX717 elicits rapid increases of BDNF and p11 in the mPFC. *P < 0.05, two-tailed Student's t-test.

The IP administration of 20 mg/kg CX717 does not change the protein level of GluA1 in the mPFC.

The intraperitoneal administration of 20 mg/kg CX717 elicits more delayed increases of the glia markers GFAP and EAAT1 in the mPFC. *P < 0.05, two-tailed Student's t-test.

CONCLUSIONS

- CX717 has a rapid, but short-lasting, antidepressant-like activity.
- CX717 does not potentiate the antidepressant response of DBS or intra-cortical infusion of (S)-AMPA, most likely because the effects of such treatments are already maximal.
- The increase in prefrontal monoamines caused by CX717 is only observed after local infusion of the drug in the mPFC. It is possible that a sustained administration of the drug is needed to alter prefrontal monoamine release.
- The rapid antidepressant-like effects of CX717 are likely caused by a fast release of BDNF and synthesis of p11.
- A delayed increase in glial markers (GFAP and EAAT1) might also contribute to these effects.

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