Repeated, 4-week dosing of CPL'36, a novel PDE10A inhibitor, does not induce tolerance to its antipsychotic-like action.

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P.1403

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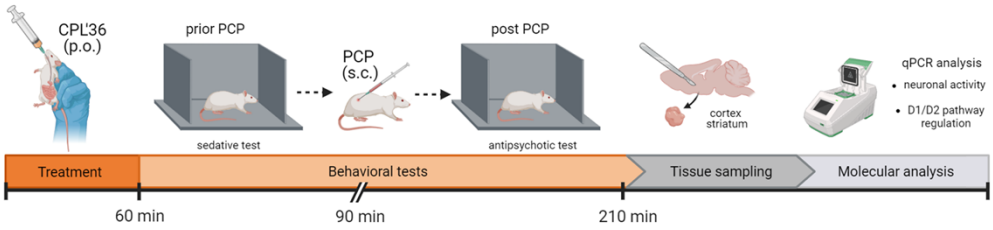
BACKGROUND

Phosphodiesterase 10A (PDE10A) inhibitors are a new class of potential antipsychotics currently undergoing clinical investigation in schizophrenia and L-DOPA induced dyskinesias in course of Parkinson's disease. PDE10A is highly enriched in the striatum, in medium spiny neurons (MSNs), where it controls intracellular cAMP and cGMP levels that are dependent on dopamine signaling. In the course of preclinical development CPL'36, a novel PDE10A inhibitor, proved to be effective in several animal models of psychotic and neuromotor disorders. However, the tolerance development to its antipsychotic and sedative action remains unknown.

In this study, we aimed to examine whether a tolerance to the antipsychotic-like (desired) and sedative (undesired side-effects) action of CPL'36 compound develops with the repeated dosing in rats. Based on the behavioral and molecular studies results, we present no tolerance effect of CPL'36 to its antipsychotic action.

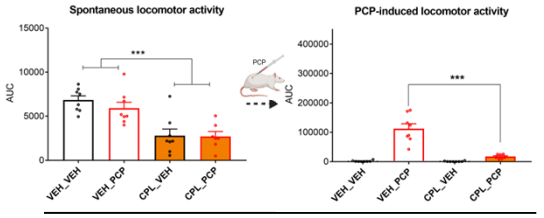
EXPERIMENTAL SCHEDULE



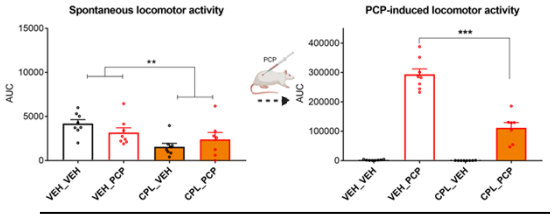
Experimental timeline. Rats were treated with CPL'36 or its vehicle (*per os; p.o.*) daily for 1 and 28 constitutive days. After the last treatment rats were placed into Opto-Varimex-4 Auto-Tracks (Columbus Instruments, Ohio, USA) sound-attenuated boxes, and were subjected to a spontaneous locomotor activity test to verify the compound sedative effect. Next, to induce hyperactivity, animals were injected with phencyclidine (PCP) or its vehicle (*subcutaneous; s.c.*) and checked for the compound antipsychotic effect. Treatment groups: 1) vehicle + vehicle; 2) vehicle + PCP (5mg/kg); 3) CPL'036 (0.6 mg/kg) + vehicle; 4) CPL'036 + PCP. After completion of the behavioral procedures striatal and cortical tissues were isolated. Then total RNA was extracted and Real-Time Quantitative PCR (qPCR) was performed to analyze neuronal activation by expression of D1/D2 activity markers *(schedule created in BioRender.com).*

RESULTS – Behavioral study

1-day treatment: CPL'36 reduces spontaneous and PCP-induced locomotion

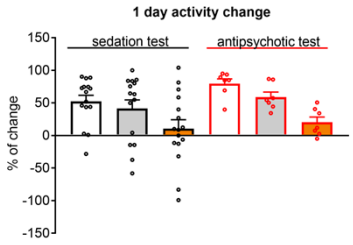


First day (Test1; T1)

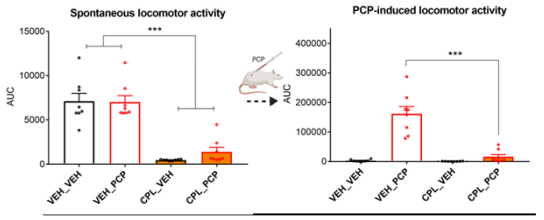


Last day (Test2; T2)

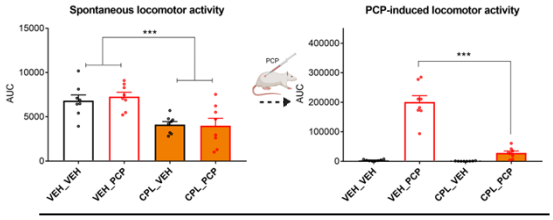
Tolerance development analysis: comparision between tests (T1 & T2)



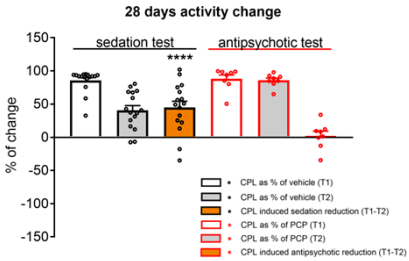
28-days treatment: After 4-weeks dosing, CPL'36 increased suppresion of PCP-induced locomotion



First day (Test1; T1)



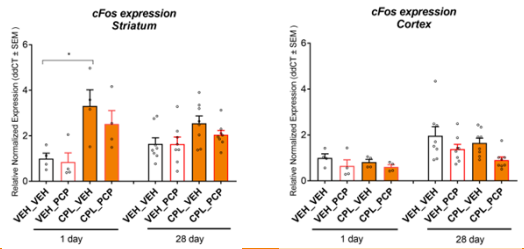
Last day (Test2; T2)



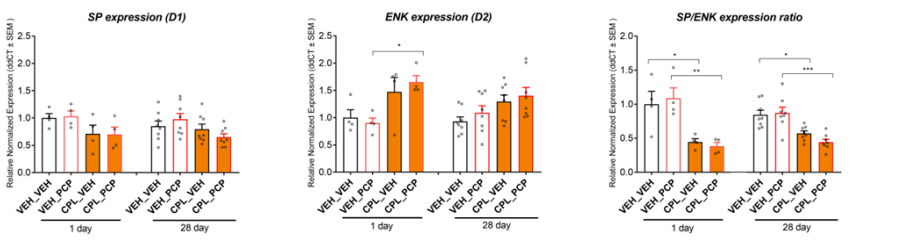
No tolerance to antipsychotic effect of the CPL'36 and tolerance to sedation after 28-days treatment

RESULTS – Gene expression

Increased *cFos* mRNA expression indicates activation of striatal MSNs

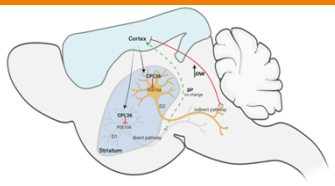


CPL'36 induced enkephalin (*ENK;* indirect pathway) mRNA expression. No changes in substance P (*SP;* direct pathway) mRNA expression level observed



SUMMARY & CONCLUSIONS

- CPL'36 prevented PCP-induced hyperlocomotion for up to 28 days following daily administration of a compound.
- No tolerance developed to CPL'36 antipsychotic-like action during the 28-day treatment.
- The compound produced significant sedation up to 28 days following its daily administration. However, after 28 days of administration, spontaneous activity suppression was significantly weaker, suggesting that tolerance to its sedative effect developed.
- CPL'36 administration induced *cFos* expression in striatal neurons indicating neuronal activation.
- The ratio of D1/D2 pathway activation (*SP*/*ENK* ratio) stays stable during the 28-day treatment with CPL'36.



DISCLOSURE

The work presented on this poster was funded partially by Celon Pharma SA. M. Matloka, P. Pankiewicz , A. Janusz and M. Górka are employees of Celon Pharma SA. J. Pieczykolan was an employee of Celon Pharma SA. M.Matloka and M. Wieczorek are coauthors of the patent.

FUNDING

The studies were cofinanced by Celon Pharma SA and the National Centre for Research and Development within the program „Path for Mazovia" (3/1.1.1/2020). Project no: POIR.01.01.01-00-0617/20-00.

European Union European Regional Development Fund

NCBR National Centre for Research and Development

European Funds Smart Growth

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