PDE4B inhibitor CV-1238 demonstrates both anti-depressant and anti-psychotic properties in preclinical models

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CONCLUSIONS

- CV-1238 is a novel, potent, and brain-penetrant PDE4D-sparing PDE4B inhibitor developed at Cerevel
- CV-1238 showed anti-depressant-like properties in the rat chronic IFNα model of depression and on EEG signatures, similarly to ketamine
- CV-1238 demonstrated effects consistent with anti-psychotic activity in the conditioned avoidance response and amphetamine-induced locomotion models
- CV-1238 potently inhibited LPS-induced TNFα secretion in human whole blood and PBMCs ex vivo

CV-1238 may be beneficial in psychiatric conditions featuring depressive and/or psychotic episodes or increased inflammation

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- Ulysses Neuroscience – IFNα study
- Psychogenics – EEG study; Conditioned avoidance response
- Charles River – Locomotor activity (San Francisco); TNFα release (Portishead)

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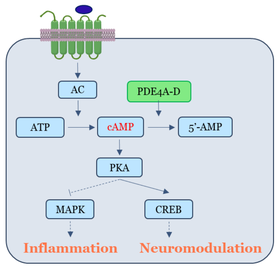
INTRODUCTION

- Psychiatric indications such as depression, schizophrenia, and bipolar disorder often show elevated pro-inflammatory marker expression in the periphery and/or central nervous system[1]
- Phosphodiesterase 4 (PDE4) is a family of enzymes that break down cAMP and have been shown to regulate inflammation and neurotransmission[2]
  - PDE4A, B, C, D isoforms: PDE4A and PDE4B highest expressed isoforms in brain
  - Non-isoform selective PDE4 inhibitors (apremilast, roflumilast): FDA-approved for peripheral indications driven by inflammation
  - Non-selective PDE4 inhibitors: Clinical proof of mechanism in CNS disease (i.e., rolipram in MDD[3], roflumilast in schizophrenia[4])
  - Utility of current PDE4 inhibitors is limited by GI side effects, thought to be at least partially driven by the PDE4D isoform[5]
- Combined immuno- and neuromodulatory activities of PDE4 inhibitors may synergize to address unmet need for various psychiatric indications



OBJECTIVE

- To characterize the PDE4B inhibitor CV-1238 in a battery of models related to depression, psychosis, and inflammation, and by EEG

METHODS

IFNα model of depression

Male Wistar rats (8-10 weeks old) were treated with 170,000 IU/kg IFNα three times a week for four weeks to induce depression-like phenotype[6]. Twenty-four hours before the forced swim test (FST), rats were treated with 5 mg/kg SC ketamine or 10 mg/kg PO fluoxetine. Alternatively, 30 minutes before the FST, rats were treated with 0.01, 0.03 or 0.1 mg/kg SC CV-1238. For the FST, rats were placed in glass cylinders filled with water and their behavior was captured for 5 min with a video camera. Results were analysed using one-way Analysis of Variance (ANOVA), followed by Fisher's least significant difference (LSD) *post hoc* test using GraphPad Prism. Outliers were identified and excluded if they were based on ± 2 standard deviations away from the group mean.

EEG recordings

Male Sprague-Dawley rats (8-10 weeks old) were implanted with DSI telemetry transmitters and subdural electrodes over the frontal cortex. EEG was recorded wirelessly from rats in their home cage. Rats were treated with 0.01, 0.03, or 0.1 mg/kg SC CV-1238, 10 mg/kg IP ketamine, 0.3 mg/kg SC rolipram, or vehicle using a Latin square study design. Power spectral density was calculated using Neuroscore for each 10 second bin for each 1 Hz from 1-200 Hz. Data were then aggregated across treatment groups, frequency bands, and 15-minute time bins. ANOVA was used to compare treatment by time bin and frequency band, followed by Dunnett's post-hoc test to compare each treatment against the mean of the Vehicle group.

Conditioned avoidance response

Adult male Wistar rats were trained for 14 days to respond to a conditioned stimulus by an electric foot shock, then injected with 0.01, 0.03, or 0.1 mg/kg CV-1238 SC or 0.3 mg/kg risperidone IP. Using a two-way shuttle box, avoidance responses were recorded when the animals moved from one compartment to the other during presentation of the conditioned stimulus and prior to foot-shock delivery. Escape failure was recorded when the animal failed to move into the other compartment during the foot shock presentation. Results were analyzed using one-way ANOVA followed by Dunnett's multiple comparisons test using GraphPad Prism software.

Amphetamine-stimulated locomotor activity

Amphetamine (2.5 mg/kg IP) was injected to male C57Bl/6J mice to increase locomotor activity, immediately followed by 0.02, 0.06, or 0.2 mg/kg CV-1238 SC or 0.1 mg/kg haloperidol SC. Locomotor activity in an open field was measured for 90 minutes by the number of beam breaks using a PAS-HC system. Results were analyzed using one-way ANOVA followed by Dunnett's multiple comparisons test using GraphPad Prism software.

LPS-stimulated TNFα release assay

Whole blood was collected from three healthy volunteers. Half of the blood was diluted with media (1:5), the other half was used for peripheral blood mononuclear cell (PBMC) isolation. Blood or PBMCs were aliquoted in 96-well plates and treated with 100 ng/mL LPS (*E. coli* O111:B4) and log dilutions of CV-1238. After incubation for 24 hours at 37°C, secreted TNFα was measured using TR-FRET assay.

RESULTS

CV-1238 exhibits anti-depressant-like properties

Decreased immobility in a model of interferon-α (IFNα)-induced depression

- Back-translational model[6]
  - Not responsive to acute SSRI treatment
- CV-1238 and ketamine reduce IFNα-induced increase in immobility in the forced swim test

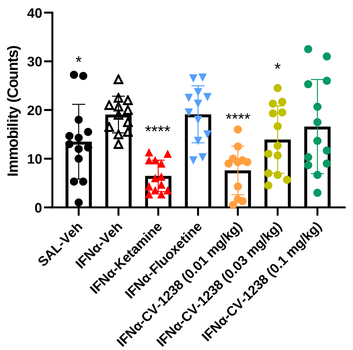


Figure 1. Quantification of immobility in the forced swim test following four weeks of IFNα administration. Statistics: ANOVA, followed by Fisher's LSD; * p<0.05; **** p<0.0001, all vs IFNα-Veh group.

Increased EEG gamma power

- CV-1238 reduced theta (2-6 hr), alpha (1-6 hr) and sigma (1-6 hr), and increased low and high gamma (1-6 hr)
  - Low gamma shown in figure
  - Similar effects of rolipram and ketamine
- Wake-promoting (not shown)

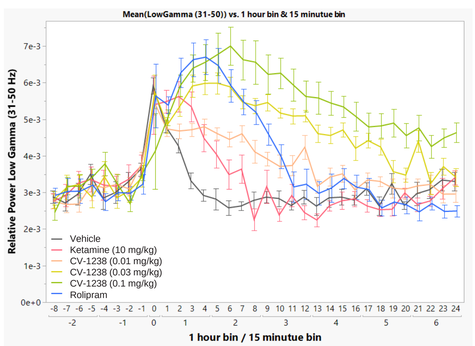
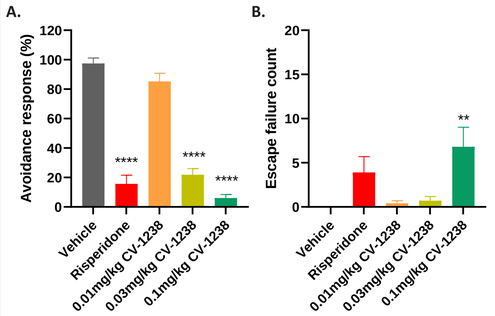


Figure 2. Quantification of EEG low gamma power over time. Statistics: ANOVA, followed by Dunnet's post-hoc test. All sleep-wake states were analyzed. Data plotted as mean ± SEM.

CV-1238 exhibits anti-psychotic-like properties

Decreased avoidance responses in conditioned avoidance response model

- Responsive to anti-psychotic treatment
- No increase in escape failures at low doses



Reduced amphetamine-stimulated locomotor activity in an open field

- Responsive to anti-psychotic treatment

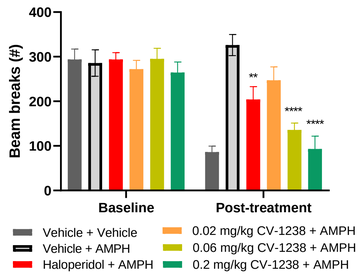


Figure 3. A. Quantification of avoidance responses. **B.** Quantification of escape failures. Data plotted as mean ± SEM. Statistics: ANOVA, followed by Dunnett's post hoc test; ** p<0.005; **** p<0.0001, all vs Vehicle group.

Figure 4. Quantification of locomotor activity at baseline and following amphetamine (AMPH) administration. Data plotted as mean ± SEM. Statistics: ANOVA, followed by Dunnett's post hoc test; ## p<0.005;#### p<0.0001, all vs AMPH group.

CV-1238 modulates inflammatory gene expression

Decreased LPS-stimulated TNFα release from human whole blood and PBMCs

- Matched whole blood and isolated PBMCs from three healthy volunteers

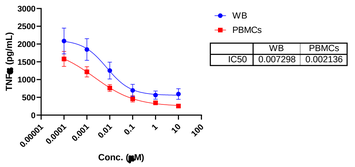


Figure 5. Quantification of TNFα levels. Data plotted as mean of the three individuals ± SEM. IC50 values calculated by 4-parameter curve fit.