Activation of KCC2 as a Novel Strategy in Development for Psychosis

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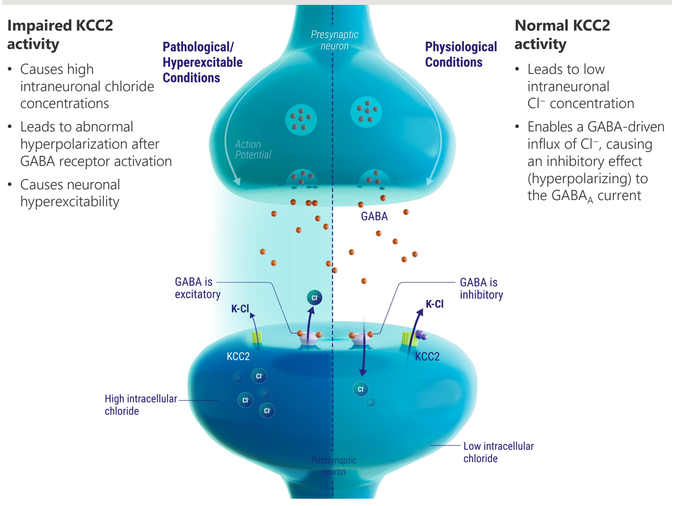
INTRODUCTION

- Dysregulation or reduction in potassium-chloride cotransporter 2 (KCC2) activity contributes to excitatory/inhibitory imbalance and converges on a broad spectrum of neurodegenerative and neuropsychiatric disorders with hyperexcitability as a core pathology[1]
- KCC2 is a neuron-specific regulator of the chloride gradient. It extrudes intracellular Cl^- to balance the Cl^- influx through activated γ-aminobutyric acid (GABA) channels and maintains GABA's inhibitory tone[2]
- Evidence of KCC2 dysfunction is implicated in schizophrenia and other diseases with neurodegeneration-associated psychosis[1,3]
- Activation of KCC2 can restore neuronal sensitivity to inhibitory neurotransmitter GABA and could potentially be targeted in diseases with an underlying excitatory/inhibitory imbalance (Figure 1)
- We investigated the potential antipsychotic effects of 2 central nervous system (CNS)-penetrant, investigational, small-molecule, KCC2 direct activators:
  - OV350, a first-in-class KCC2 direct activator administered intravenously
  - OV4071, the first oral KCC2 direct activator

Figure 1. Mechanism of action: Direct activation of KCC2 restores excitatory/inhibitory balance via GABAergic inhibition



KCC2 direct activation improves chloride extrusion and thereby GABAergic inhibition

GABA, γ-aminobutyric acid; $GABA_A$, γ-aminobutyric acid subtype A; KCC2, K^+-Cl^- cotransporter 2.

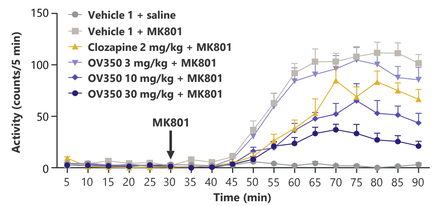
RESULTS

OV350: An Intravenous KCC2 Direct Activator

OV350 has antipsychotic properties and is nonsedating in preclinical models

- The SmartCube® platform analysis showed (data on file, not shown):
  - Predominantly atypical antipsychotic drug-like activity
  - No sedation or other adverse behavioral effects up to 75 mg/kg

Figure 2. Dose-dependent effect of OV350 on MK801-induced hyperlocomotion



Data represent mean±standard error of the mean of 10 mice/group. After MK801 administration, a statistically significant decrease in hyperlocomotion was observed in the groups treated with OV350 10 mg/kg and 30 mg/kg doses vs the vehicle control starting at 25 min after administration (55-min time point; $P<0.05$). ANOVA, followed by post-hoc Dunnet test was used for the analysis. Clozapine, an atypical antipsychotic, was included as a positive control.

OV350 suppresses hyperlocomotion in MK801-induced mouse model of psychosis

- The noncompetitive NMDA receptor antagonist MK801-induced hyperlocomotion model mimics psychosis-like behavior mediated through reduced GABAergic inhibition[4]
- OV350 (intraperitoneal injection) suppressed MK801-induced hyperlocomotion in a dose-dependent manner (Figure 2)
- No motor impairment was observed with OV350 at the maximum feasible dose (60 mg/kg intraperitoneal injection) evaluated in the rotarod test (data on file)
- OV350 pharmacokinetic (PK) and pharmacodynamic (PD) analyses estimated an in vivo half-maximal effective concentration (EC_{50}) of 719.3 ng/mL (data on file)
- OV350 also suppressed phencyclidine (PCP)-induced hyperlocomotion in a dose-dependent manner in a PCP-induced model. Significant effects were seen with 10 mg/kg and 30 mg/kg doses (data on file)

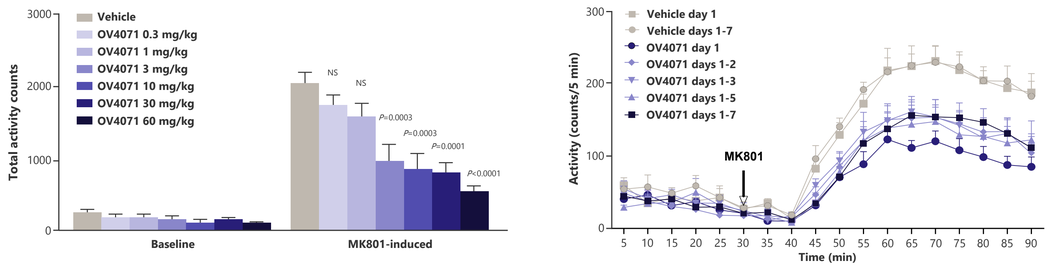
OV4071: An Oral KCC2 Direct Activator

- OV350 data supported advancement of OV4071, a pharmacologically more potent KCC2 direct activator with consistent plasma exposure and CNS penetration (20 times the potency of OV350; data on file)

OV4071 suppresses hyperlocomotion in MK801-induced mouse models of psychosis

- Similar to OV350, administration of OV4071 was effective in the psychosis model and returned locomotion to natural levels (data not shown) in a dose-dependent manner; rapid single-dose effects were maintained upon repeated dosing (Figure 3)
- OV4071 PK/PD analysis estimated an in vivo EC_{50} of 44.2 ng/mL (data on file)

Figure 3. (A) Robust single-dose, dose-effect and (B) sustained effect of repeated dosing of OV4071 on MK801-induced hyperlocomotion



Data represents mean±standard deviation. NS, not significant.
(A) Mice were pretreated with OV4071 or vehicle and administered MK801 0.3 mg/kg after 30 minutes.
(B) Mice received OV4071 3 mg/kg or vehicle once daily up to 7 days before MK801 0.3 mg/kg administration.

CONCLUSIONS

- The direct KCC2 activators OV350 and OV4071 penetrate the brain (data on file) and show physiologic activity in preclinical models used to study psychotic disorders
  - Both OV350 and OV4071 exhibited robust antipsychotic-like activity by significantly reducing MK801-induced hyperlocomotion in a dose-dependent manner
  - Activity of OV4071 in the MK801 model was maintained with once-daily administration over 7 days, demonstrating a persistent pharmacologic effect that supports its potential for long-term treatment
  - Effects of direct KCC2 activation in the MK801 model appeared comparable to or greater than those observed with the atypical antipsychotic clozapine
  - No signal of sedation or adverse behavioral effects with OV350 or OV4071 were observed (data on file)
- Taken together, these results highlight a mechanism that engages pathways central to the pathophysiology of psychosis and show the potential of KCC2 activator OV4071 in suppressing hyperlocomotion without causing motor impairment
- Although further studies are needed to establish its clinical relevance, the emerging evidence suggests that KCC2 direct activation may offer a new therapeutic avenue for the treatment of psychotic disorders

FUTURE PERSPECTIVE: Advancing KCC2 Direct Activation Toward Clinical Evaluation in Psychosis

- In schizophrenia, glutamate-driven excitation in the prefrontal cortex contributes to surges in striatal dopamine, contributing to positive (psychosis), negative, and cognitive symptoms[3,5]
- KCC2 activation can enhance GABAergic inhibition, thus counteracting prefrontal hyperexcitation and downstream dopaminergic sequelae, which is thought to:
  - Reduce psychosis due to a dopaminergic surge in the striatum
  - Improve negative symptoms (e.g., amotivation, social withdrawal)
  - Rescue cognition through a preservation of dopaminergic function in the prefrontal cortex

Schizophrenia: Potential role of KCC2 activator

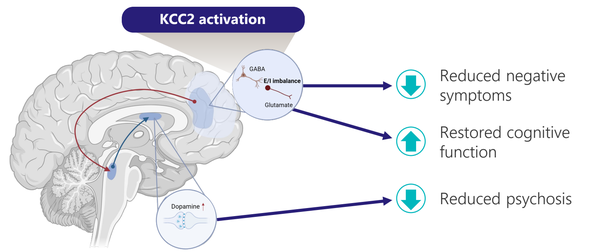


Figure adapted from Howes and Shatalina, *Biol Psychiatry.* 2022,[3] with permission under the Creative Commons CC-BY 4.0 license.
E/I, excitatory/inhibitory; GABA, γ-aminobutyric acid.

OV4071 clinical development

- Based on encouraging preclinical (OV350 and OV4071) and clinical (OV350; data on file) data, a phase 1, randomized, double-blind, placebo-controlled, ascending single- and multiple-dose study assessing the safety, tolerability, PK, and PD of OV4071 in healthy participants has been initiated
- A phase 2 study in participants with schizophrenia is planned for 2027

References

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Disclosure

The information presented in this poster concerns a use that has not been approved by the U.S. Food and Drug Administration.

Author Disclosures

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