Abstract

CTP-692, a deuterated version of the naturally occurring amino acid D-serine, is being developed as an adjunctive treatment for schizophrenia. CTP-692 and D-serine both bind to the glycine modulatory site of the human NMDA receptor (NMDAR), with indistinguishable affinities and produce similar functional activation of the NMDAR in the presence of glutamate. In some human clinical studies, D-serine has demonstrated benefits on negative and cognitive symptoms of schizophrenia, as well as effects on positive symptoms. However, the use of D-serine as a human therapeutic may be limited by concerns regarding nephrotoxicity observed in rats. CTP-692 provides greater AUC exposure and a longer half-life than the corresponding dose of D-serine, as expected for deuterium-modified compounds. Notably, important markers of nephrotoxicity, serum creatinine and blood urea nitrogen, were highly elevated in rats dosed with D-serine but were within normal values with CTP-692 dosing. Based on the improved pharmacokinetic and toxicological profiles in rats, CTP-692 may provide an improved therapeutic window compared to D-serine while preserving the intrinsic pharmacology of NMDAR. Phase 1 clinical testing of CTP-692 is expected to begin by year-end 2018.

Introduction

Deuterium (a non-radioactive isotope of hydrogen) is very similar to hydrogen except that the mass is twice that of hydrogen. Because of the increased mass, deuterium forms a chemical bond with carbon that is stronger than the carbon-hydrogen bond. In some cases, deuterium modification will decrease the rate of metabolism as a result of slower carbon-deuterium bond cleavage resulting in reduced metabolic stability. Foster, Shen, and Foster, 1985; Shen, 2010. In select cases, the new molecule with deuterium modification has enhanced metabolic properties while preserving the intrinsic pharmacological activity. This has been significant interest in the use of D-serine for the treatment of schizophrenia but development has been limited because of concerns of nephrotoxicity. Here we describe that selective substitution in D-serine for the treatment of schizophrenia may be limited because of concerns of nephrotoxicity. For the binding affinity of D-serine to deuterium (resulting in CTP-692) did not change the compound's ability to co-activate the NMDA receptor, but increased preclinical metabolic stability and remarkably decreased markers of toxicity on acute dosing in vivo.

For all experiments described here, D-serine was purchased from Sigma-Aldrich while CTP-692 was supplied by Concert Pharmaceuticals, Inc.

CTP-692 and D-serine have similar intrinsic pharmacology

The binding and activation of receptors by D-serine and CTP-692 were similar in all cases where they were measured. Compared to the non-deuterated compound, CTP-692 demonstrated nearly identical in vitro binding affinity for the glycine modulatory site of NMDAR. For the binding affinities of CTP-692 to the glycine site of NMDAR receptor from rat cerebral cortical membranes, the average K for CTP-692 was 0.015 μM while the average K for D-serine was 0.05 μM.

CTP-692 and D-serine have similar activity at the NMDA receptor

The activation of the NMDA receptors by CTP-692 and D-serine was assessed in an automated patch clamp system (ScrenPatch) using HEK293 cells expressing human NMDA subunits GluN1 and GluN2A. Cells were treated with increasing concentrations of CTP-692 or D-serine (0.003 to 30 μM). Peak current and steady state current were measured. The activity at the NMDA receptor was indistinguishable for the two compounds. A representative graph is depicted.

Mean PO Rat PK (Linear)

CTP-692 has a greater t1/2, Cmax, and AUC, and a similar tmax and %F as D-Serine when dosed PO in rats

Sprague-Dawley Rats were dosed with CTP-692 or D-serine PO at 10 mg/kg in 0.5% Dextrose. Plasma levels of CTP-692 and D-serine were evaluated using non-compartmental (NCA) PK. Greater exposure and a longer half-life are observed in rats dosed with CTP-692 vs D-serine with both IV (not shown) and PO dosing.

CTP-692 accumulates in the rat forebrain (site of action)

After dosing rats with CTP-692 PO at 100 mg/kg, 24 hours after dosing. In all cases the AUC and Cmax for each dose group was larger for the rats dosed with CTP-692 vs D-serine. A representative graph is depicted.

Conclusions

• CTP-692 and D-serine have similar intrinsic pharmacology at the NMDA receptor.
• CTP-692 is more resistant to metabolism than higher systems. Both may be reached with the same dose.
• CTP-692 has a larger %F in the preclinical species tested (rat and dog).
• CTP-692 accumulates at the site of action (forebrain) in the rat.
• CTP-692 appears less nephrotoxic in rats as measured with creatinine and BUN.

Normal BUN and creatinine levels observed in rats dosed with CTP-692

Rats were dosed PO with either CTP-692, D-serine or vehicle. Rats were dosed in 100 mg/kg increments from 150 mg/kg to 750 mg/kg with either CTP-692 or D-serine. Serial PK was collected to confirm exposure. Clinical chemistry and Blood Urea Nitrogen was performed 24 hours after dosing. In all cases the AUC and Cmax for each dose group was larger for the rats receiving CTP-692 vs D-serine. The AUC was dose-linear for both CTP-692 and D-serine. However, the Creatinine was dose-linear above ~400mg/kg. For both compounds, none of the rats showed visible clinical signs at the doses tested.

Mean Rat PK PO (Semi Log)

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Literature cited


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CTP-692: Selective deuterium modification of D-serine markedly decreases renal toxicity in preclinical testing