CTP-692, a Novel Deuterium-Modified D-serine, Produces Higher Brain Exposure in Rats Compared to D-serine

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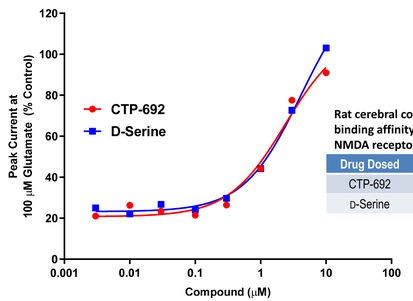
Abstract

Schizophrenia is associated with low levels of D-serine, the most important synaptic co-agonist of the N-methyl D-aspartate (NMDA) type glutamate receptor in the brain. Currently-approved schizophrenia drugs predominantly modulate D_2, or D_2 and 5-HT_{2a} receptors. Neurobiological and genetic findings link NMDA receptor hypofunction to the etiology of schizophrenia. Treatment of patients with schizophrenia with the NMDA receptor co-agonist, D-serine, has been reported to result in improvement in positive and negative symptoms and cognitive dysfunction. A potential limitation to the development of D-serine as a therapeutic is that it causes renal toxicity in rats at exposure levels similar to those reported to result in therapeutic effects in humans. In a direct comparative study, rats acutely dosed with D-serine exhibited increased serum creatinine and blood urea nitrogen, indicating renal toxicity, whereas CTP-692 did not cause changes in these blood markers. While the binding and functional activity of CTP-692 at the glycine site of the NMDA receptor are nearly identical to those of D-serine, deuterium modification resulted in greater plasma and brain exposure of CTP-692 vs D-serine in rats. CTP-692 had linear exposure (AUC) for doses ranging from 150 mg/kg to 2000 mg/kg in rats and plasma steady state was achieved by Day 2. However, at Day 4, brain levels are still increasing as steady state had likely not yet been achieved. After 4 days of dosing, the exposure of CTP 692 in rat forebrains was ~1.7 times greater than D-serine. Because of the slow uptake and clearance of CTP-692 from rat brains, fluctuations in brain levels upon dosing CTP-692 are minimized. Based on IV and PO PK profiles in both rats and dogs, the oral bioavailability of CTP-692 was >80%. Additionally, CTP 692 is well suited for adjunctive use as it is neither a CYP inhibitor nor a CYP substrate. In summary, based on these rat studies, CTP-692 is a potential first-in-class adjunctive treatment for schizophrenia that offers the pharmacological advantages of treatment with D-serine but with the potential for lower risk of renal toxicity, higher brain exposures and efficacy at lower doses.

CTP-692 and D-Serine have Similar Pharmacological Properties

CTP-692 and D-serine have nearly identical binding affinity to the glycine modulatory site of NMDA receptor in rat cortical membranes

CTP-692 and D-serine have nearly identical potencies with respect to *in vitro* NMDA receptor activation as measured in an automated patch clamp system (ScreenPatch®) using HEK293 cells expressing human NMDAR subunits GluN1 and GluN2A.

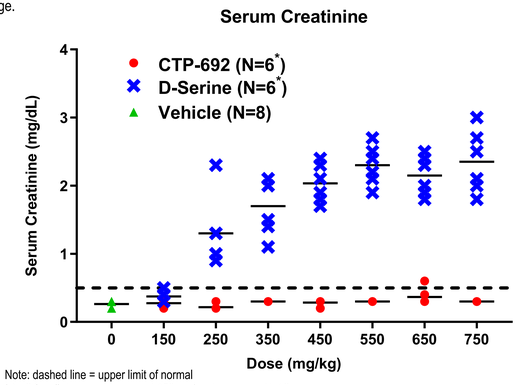


Rat cerebral cortical membrane binding affinity at glycine site of NMDA receptor

Drug Dosed	K_i (μM)
CTP-692	0.91
D-Serine	0.95

CTP-692 has an Improved Renal Safety Profile in Rats

Rats were dosed PO with either vehicle (0.5% methylcellulose in water), CTP-692, or D-serine. Clinical chemistry was performed 24 hours after dosing. The known renal toxicity markers of D-serine were evident starting at 250 mg/kg. CTP-692 had no effect on creatinine or BUN (data not shown) over the same dose range.



Note: dashed line = upper limit of normal
* N=6 for all dose groups except 150 mg/kg dose group N=12

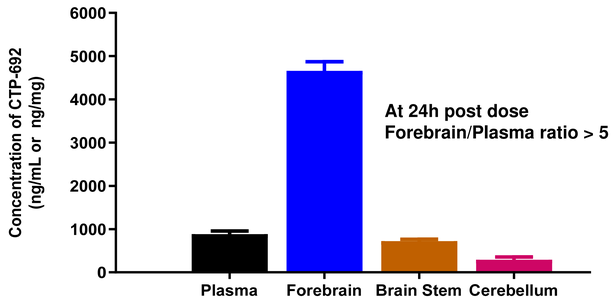
CTP-692 is Orally Bioavailable in Both Rat and Dog

CTP-692 was dosed IV and PO to both male Sprague Dawley rats and Beagle dogs. An oral bioavailability above 80% was obtained in both species.

	Dose (mg/kg)		$AUC_{0-\infty}$ (ng*h/mL)		%F
	IV	PO	IV	PO	
Rat (SD)	5	10	9980	21500	93%
Dog (Beagle)	5	10	23500	40900	87%

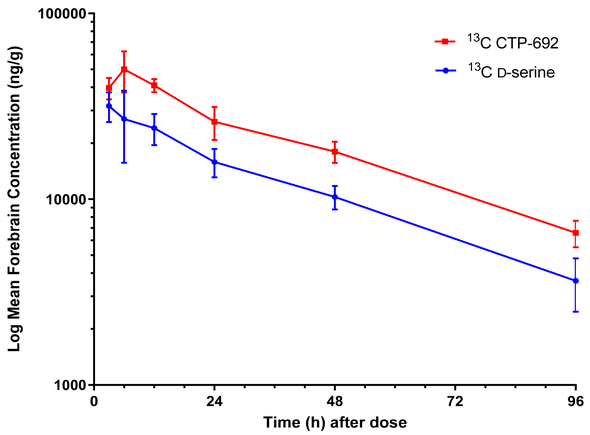
CTP-692 Concentration is Higher in the Rat Forebrain

CTP-692 was formulated in 0.5% methylcellulose in water and administered orally to male Sprague Dawley rats at 100 mg/kg as a single dose (N=4). Twenty four hours after dosing, animal brains were collected and sectioned into forebrain, brain stem, and cerebellum for analysis.



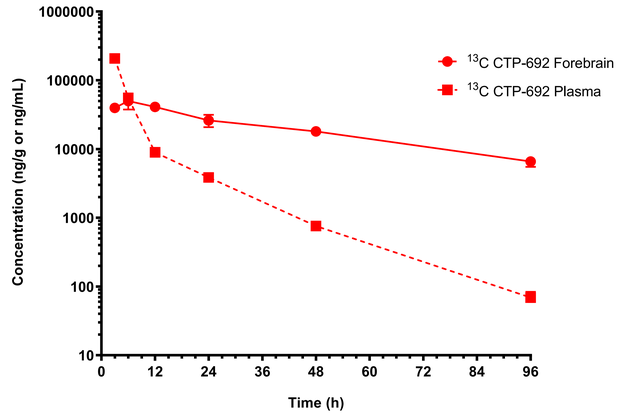
CTP-692 has Improved Forebrain Exposure vs D-Serine in Rats

To distinguish exogenous from endogenous D-serine, both D-serine and CTP-692 were labeled with carbon-13 and administered PO to rats. Rats were perfused and forebrains collected at different times to determine exposure of CTP-692 and D-serine. CTP-692 had a 1.7x greater AUC exposure vs D-serine in rat forebrain.



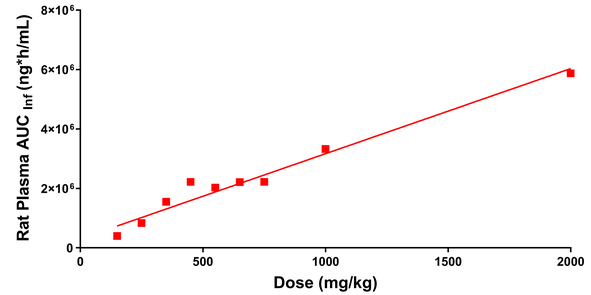
CTP-692 has an Extended Half-Life in Brain vs Plasma in the Rat

CTP-692 was administered orally to male Sprague Dawley rats at 400 mg/kg. Brains and plasma were collected. CTP-692 concentrations in plasma and forebrain were measured by LC-MS. Clearance from the rat forebrain is much slower than clearance from the plasma.



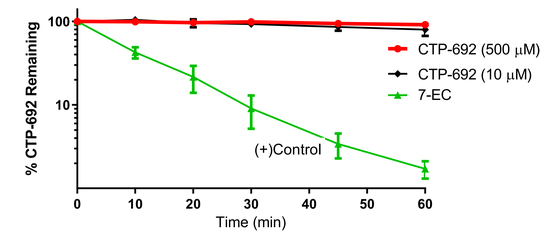
CTP-692 Plasma Exposure is Linear Over a Wide Range After Oral Administration to Rats

CTP-692 was dosed PO to Sprague Dawley rats and the plasma AUC was linear from 150-2000 mg/kg. C_{max} was infra-proportional with dose (data not shown).



CTP-692 Does Not Affect CYP Enzymes

CTP-692 was incubated in human liver microsomes. Minimal CYP metabolism was observed while the positive control was consumed as expected. Additionally, CTP-692 does not inhibit CYP 1A2, 2C8, 2C9, 2C19, 2B6 ,2D6 and 3A4 (data not shown).



Conclusions

CTP-692 has the potential to be an ideal adjunctive treatment for schizophrenia:

- Nearly identical pharmacology (binding and activation of NMDA receptor) to D-serine
- Reduced nephrotoxicity compared to D-serine, as measured by serum renal safety markers in the rat
- Good oral bioavailability and linear PK over a wide range of doses
- The CTP-692 concentration is higher in the rat forebrain where the target NMDA receptors reside
- CTP-692 has increased rat forebrain exposure vs D-serine
- Slow brain uptake/clearance minimizes fluctuations in brain exposure
- Low probability for drug-drug interactions since CTP-692 is neither a substrate or inhibitor for CYP enzymes

For further information

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