Preclinical Pharmacodynamic and Pharmacokinetic Characterisation of HTL-A, a Selective GPR52 Agonist

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Background

- GPR52, a Gs coupled orphan receptor, has been proposed as a target for the treatment of positive, negative and cognitive symptoms of schizophrenia. High expression of the receptor on dopamine D2 receptor-expressing medium spiny neurons and D1 cortical neurons[1] suggests that a GPR52 agonist will selectively modulate dopaminergic and glutamatergic signalling without causing the adverse effects associated with antipsychotics.
- In the current studies, the pharmacokinetic properties of HTL-A, a selective GPR52 agonist (pEC50 7.5), were measured in preclinical species and pharmacodynamic effects were explored in the rat subchronic PCP-induced cognitive deficit model. A neurobehavioural (Irwin) test was performed following repeat dosing to evaluate potential adverse nervous system effects.

Methods

1. In vivo pharmacokinetic studies of HTL-A were performed following intravenous and oral administration in Sprague-Dawley rats, beagle dogs and cynomolgus monkeys. Brain penetration was assessed in rats.
2. Reversal learning was performed in adult female Lister Hooded rats treated with PCP (2 mg/kg) or saline IP twice daily for 7 days, followed by >7 days washout. Rats underwent operant training firstly to press the left/right lever for a food reward in to the presence or absence of a visual cue, and then to respond to the opposite contingency. Rats were treated with HTL-A (1, 5 or 15 mg/kg, PO, in the first study and 3, 10 or 30 mg/kg, PO in the second study) and 2 hours later underwent the reversal learning task. In the initial phase, the reward contingency was the same as the previous day and in the reversal phase the reward contingency was reversed.
3. The CNS safety pharmacology profile of HTL-A was evaluated in Wistar rats on days 2, 5 and 10 of treatment with HTL-A (10, 30 and 100 mg/kg/day, PO). General behaviour, reflexes and body temperature were recorded 2 h using the Irwin test in the rat. Catalepsy was measured 2 h following acute treatment using the four wood peg test; haloperidol (1 mg/kg, sc) was included as a positive reference agent.

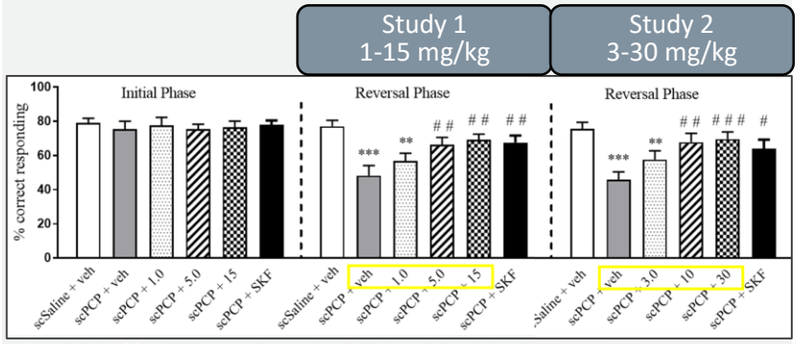
Results

1. HTL-A demonstrates excellent pharmacokinetic properties across preclinical species

Allometric scaling from preclinical species predicts low clearance and long half-life in human. Kp,uu in rat was 0.35.

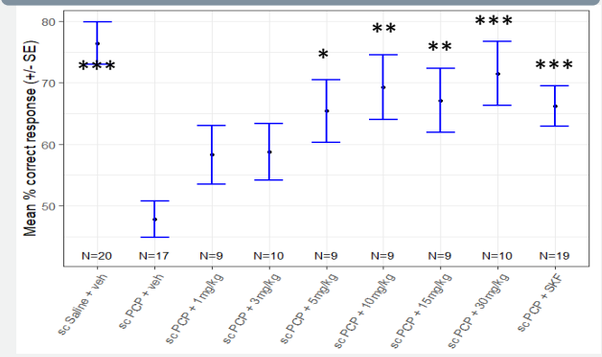
Species	Clearance (ml/min/kg)	Volume (L/kg)	t½ (h)	Bioavailability (F)
Rat	16	1.0	0.8	50%
Dog	12	1.1	1.3	59%
Monkey	2	1.4	6.8	81%

2. HTL-A reversed the subchronic PCP-induced deficit in the reversal learning task across a wide dose-range



**p<0.01, ***p<0.001 vs scSaline; #p<0.05 ##p<0.01 ###p<0.001 vs scPCP control group.

Meta-analysis of 2 reversal learning studies



One-way ANOVA was performed on Arc-Sin transformed data to detect main effect of drug treatment in the initial and reversal tasks. Where a significant effect was detected, a post-hoc LSD t-test was performed to compare treatment groups vs the appropriate control in the reversal phase. *p<0.05, **p<0.01, ***p<0.001 vs scPCP control group.

Results – continued

3. No neurobehavioural adverse effects were observed following acute or repeated treatment with HTL-A

HTL-A did not cause catalepsy following acute treatment at 10, 30 or 100 mg/kg, PO. No effects were observed in the Irwin test following treatment for 2, 5 or 10 days at 10, 30 or 100 mg/kg/day, PO.

Conclusions

- HTL-A demonstrates excellent pharmacokinetic properties across preclinical species, with predicted low clearance and good bioavailability in human.
- HTL-A reversed the PCP-induced deficit in the reversal learning task, a measure of cognitive flexibility. The effects were consistent across two separate studies and a meta-analysis of the data supported efficacy of HTL-A at 5-30 mg/kg, PO.
- No adverse effects were observed in the Irwin test and differentiation from haloperidol was demonstrated in the catalepsy test.
- Overall, these studies support the progression of HTL-A as a safe treatment for cognitive dysfunction in patients with psychotic disorders.

References

[1]Komatsu et al. PLoS One. 2014, 28; 0(2):e90134

Contact & Disclosures

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CMS, SP, NA, AM, AB, MB and SW are employees of Sosei Heptares. The authors declare that no other competing interests exist.

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