Transcranial Magnetic Stimulation as a Translational Biomarker for Modulation of AMPA Receptor Function

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Introduction

- Enhanced AMPA receptor–mediated signaling is hypothesized to be a key component in the rapid-acting antidepressant effect of the non-competitive NMDA receptor antagonist ketamine[1].
- TAK-653 is an AMPAkine (AMPA receptor positive allosteric modulator) being developed for treatment-resistant depression (TRD).
- Confirmation of target engagement and demonstration of pharmacological effects of AMPAkines at safe and relevant plasma exposures have remained elusive. Additionally, there has been little progress in identifying neurocircuitry modulation biomarkers for glutamate-based pharmacology, highlighting the need for the development of a translational circuit-based pharmacodynamic biomarker.
- In this context, transcranial magnetic stimulation (TMS) of the motor cortex was applied in rats and humans, with TMS-elicited mechanomyogram (MMG) amplitudes[2] and motor-evoked potentials (MEPs) in humans, as peripheral biomarkers for cortical excitability in each species, respectively.

Overall Objective

- To test whether TMS-evoked motor responses assessed with MMG or electromyography (EMG) can be modulated by AMPA receptor activation (via TAK-653) in both rats and humans.

Animal Studies

Objective

- To test whether TMS-induced MMG amplitudes increase in rats following administration of TAK-653 compared to vehicle.

Methods

- Male Sprague Dawley rats (n=51) were administered vehicle or TAK-653 (0.1, 0.3, 1.0, 8.0, and 50.0 mg/kg) via oral gavage.
- Blood and brain levels of TAK-653 were assessed at each dose (n=20).
- Corticospinal excitability was assessed using single-pulse TMS (spTMS) (n=31):
  - Pentobarbital (25 + 15 mg/kg, i.p., 30 min apart) and straps (**Figure 1A**) were used for restraint.
  - Three-dimensional acceleration vectors (**Figure 1B**) were used post hoc to calculate MMG amplitudes (**Figure 2**) in the form of voltage [$\sqrt{(x^2+y^2+z^2)}$].

Figure 1. Rat Undergoing TMS Procedure

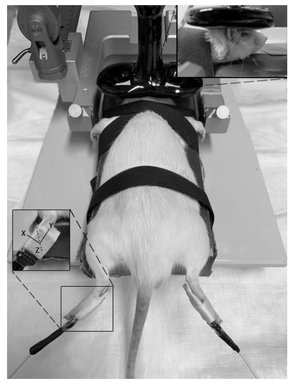
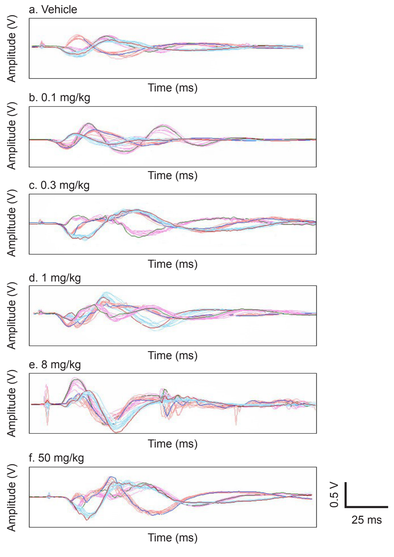
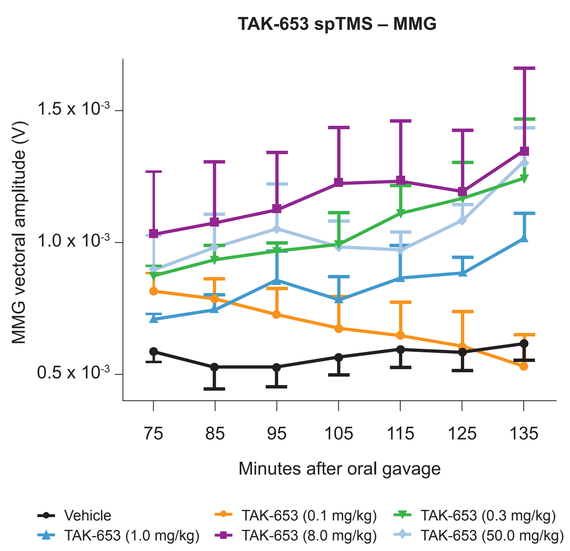


Figure 2. Electromyography Graph Illustrating a Sample Waveform in Rat



To our knowledge, this study is the first to demonstrate a translational physiological assessment of neural circuitry responses to an AMPAkine.

Figure 3. TAK-653 TMS-Induced MMG Amplitudes in Rats



Results

- TAK-653 enhanced TMS-induced MMG amplitudes in rats by 30%-70% at all doses except 0.1 mg/kg (**Figure 3**; **Table 1**).
- Mean TAK-653 plasma levels at effective doses 2 h post dose were all ≥5.74 ng/mL (**Table 2**).

Table 1. ANOVA Summary Table for Rats

	F (DFn, DFd)	*P* value
Time x Dose	F (30, 150) = 1.692	0.0215
Time	F (2.475, 61.87) = 4.076	0.0152
Dose	F (5, 25) = 4.399	0.0052
Animal	F (25, 150) = 15.96	< 0.0001

Table 2. Rat TAK-653 Mean Plasma Levels With the Effective Doses 2 h Post Dose

TAK-653 Dose* (mg/kg)	2 h Post Dose (ng/mL)
0.3	5.74
1.0	64.70
8.0	259.00
50.0	470.00

*0.1 mg/kg dose had no effect.

Conclusion

- Compared to vehicle, TAK-653 acutely increased corticospinal excitability in rats.

Human Studies

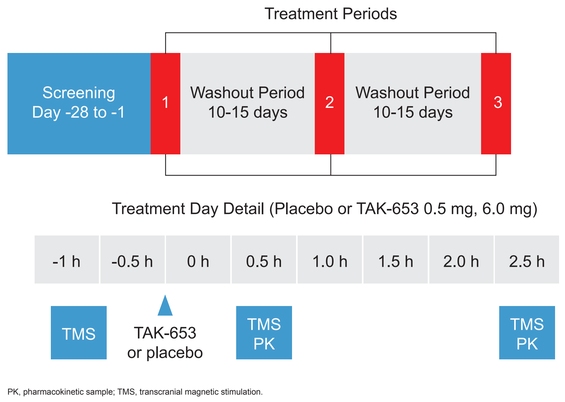
Objective

- To assess TMS-elicited MEP responses as a translational biomarker for neural circuit modulation by TAK-653 in humans.

Methods

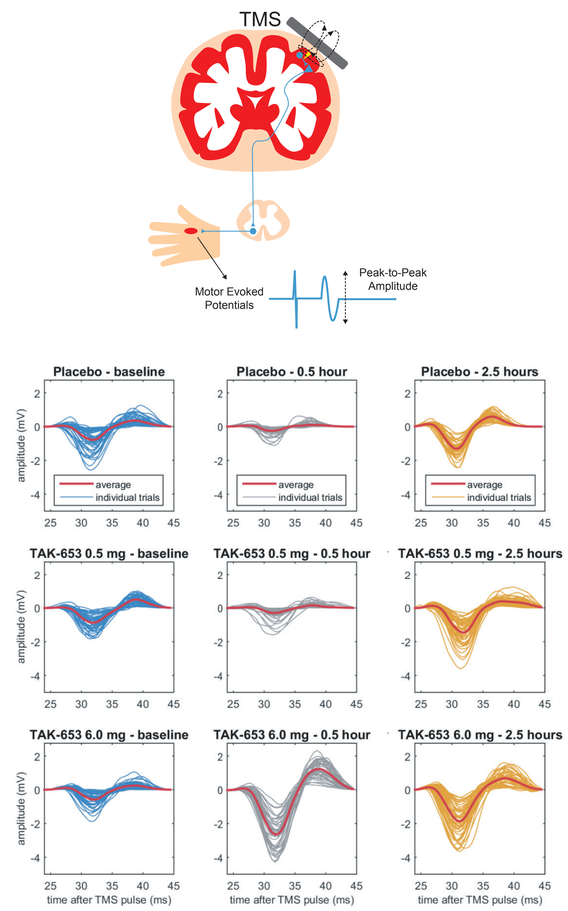
- 24 healthy volunteers participated in a randomized, double-blind, placebo-controlled, three-way crossover study (**Table 3**; **Figure 4**).
- Each subject was administered placebo or TAK-653 (0.5 mg or 6.0 mg) in a given period.
- TMS assessments were performed at baseline (pre-dosing) and at 0.5 and 2.5 hours post-dosing
  - Fifty single pulses at 120% of baseline resting MT (rMT) were applied to the primary motor cortex (**Figure 5**).
- An a priori criterion for success was set as a statistically significant difference in change from baseline with either dose compared to placebo at 2.5 hours post-dosing for either of two primary endpoints (peak-to-peak amplitude of MEPs or rMT).

Figure 4. Human Study Design



PK, pharmacokinetic sample; TMS, transcranial magnetic stimulation.

Figure 5. TMS of the Corticospinal Tract and Sample TMS-Induced MEPs in Humans



Results

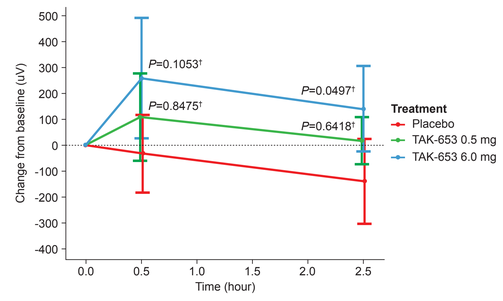
- A 6.0 mg dose of TAK-653 showed a statistically significant increase in average peak-to-peak MEP amplitude from pre-dose to baseline compared with placebo (**Figure 6**).
- A 0.5 mg dose of TAK-653 also showed an increase in MEP amplitude, but the change compared with placebo was not statistically significant.
- There were no significant changes in rMT from pre-dose baseline compared with placebo (**Figure 7**).
- Mean TAK-653 plasma levels at 0.5 and 2.5 hours post dosing were 0.99 ng/mL and 4.19 ng/mL for 0.5 mg and 2.57 ng/mL and 45.99 ng/mL for 6.0 mg, respectively.
- All adverse events were mild to moderate in intensity, and no serious adverse events occurred.

Table 3. Analysis Population and Demographics

	Total (N=24)[a]
Age (years)	
Mean (±SD)	27.9 (9)
Minimum-maximum	20-49
Gender, n (%)	
Male	23 (96)
Female	1 (4)
Race, n (%)	
Caucasian	22 (92)
Black*	1 (4)
Asian	1 (4)
Other	n/a
BMI: Mean (±SD), kg/m²	23.9 (3)

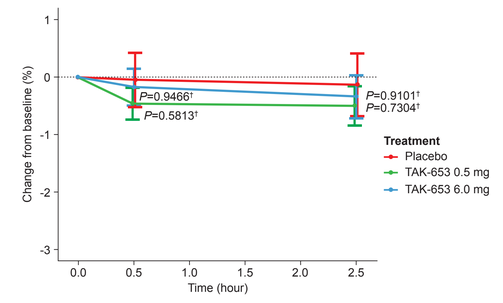
[a]All human analyses included 24 subjects except change of MEP 6.0 g dose, which only included 23 of the 24.
*Black and white biracial subject counted once as black.

Figure 6. Mean and SE of Change from Baseline in Peak-to-Peak Amplitude of MEP



†*P* values of the test on the difference in least-squares means using Dunnett's multiple comparison method.

Figure 7. Mean and SE of Change from Baseline in Resting Motor Threshold (rMT)



†*P* values of the test on the difference in least-squares means using Dunnett's multiple comparison method.

Conclusions

- TAK-653 produced a pharmacodynamic effect in rats, with a significant increase in MEP amplitude compared with vehicle at doses yielding 5.74 ng/ml in plasma or higher.
- TAK-653 also produced a pharmacodynamic effect in humans, with a statistically significant increase in MEP amplitude compared to placebo with the 6 mg dose, but not 0.5 mg.

References

1. Moghaddam, B., et al. Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. *J Neurosci*. 1997;17(8):2921-2927.
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Disclosures

Patricio O'Donnell, Quanhong Lei, Derek L. Buhl, Martin Lubell, Mahnaz Asgharnejad, Venkatesha Murthy, and Laura Rosen are employees of Takeda Pharmaceuticals International, Inc., Cambridge, MA. Lin Xu was employed by Takeda at the time of these studies.

Gabriel Jacobs, Rob Zuiker, Francis Dijkstra, Titia Ruijs, and Annika de Goede are employees of Centre for Human Drug Research (CHDR) in Leiden, the Netherlands.

Annika De Goede is also an employee of the University of Twente with the Clinical Neurophysiology (CNPH) group in Enschede, the Netherlands. If employment status is his only disclosure, you can edit sentence to state: Ugur Damar and Andres Pascual-Leone are employed by Boston Children's Hospital, Harvard Medical School, Boston, MA.

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