TSND-201 (Methylone): A Rapid-Acting Neuroplastogen that Stimulates Neurite Outgrowth

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Introduction

Post-traumatic stress disorder (PTSD) affects 12 million adults in the United States annually, yet current treatment options - psychotherapy or selective serotonin reuptake inhibitors (SSRIs) - show limited efficacy. TSND-201 (methylone), a rapid-acting neuroplastogen currently under investigation in randomized clinical trials, demonstrates rapid, robust, and long-lasting therapeutic benefits for individuals with PTSD.

The current study was undertaken to elucidate molecular mechanisms underlying methylone's robust and durable effects observed in clinical and preclinical studies.

About TSND-201 (methylone)

Highly selective NE, 5HT, DA releaser and neuroplastogen

- Rapid release of neurotransmitters (NE > 5HT > DA) [1,2]
- No off-target activity at 168 G-protein coupled receptors, including 5HT2A[1]
  - Non-hallucinogenic in humans[3] and animal models[4]
  - No inhibition of VMAT2[5], no depletion of 5HT or DA[2]
- Rapid induction of neuroplasticity-related genes (e.g., BDNF) in brain areas underlying PTSD, MDD, and anxiety[1]

Rapid, robust, long-lasting beneficial effects in animals

- Improves fear extinction (FE) and recall[4,6]
- Increases center time in the open field test[7]
- Reduces immobility by ~95% in forced swim test (FST)[7]
- Effect in FST persisted for at least 72h after a single dose[7]
- Antidepressant-like benefit in stress models (social defeat, learned helplessness, sucrose preference)[8]

Response in FE and FST is not changed by prior SSRI administration[6,7]

Well-tolerated in healthy human volunteers[3,9,10]

Rapid, robust, and durable efficacy in an open-label study of PTSD patients[11]

- 14 participants with severe PTSD were treated once weekly with TSND-201 for 4-weeks and were followed for 6-weeks after last dose
- CAPS-5 scores decreased by 8.4 points after dose 1 (day 3); 23.3 points after dose 2 (day 10); and 36.2 points at the end of study (day 64)
- Remission was achieved in 61.5% of participants at the end of study

Randomized, placebo-controlled study (IMPACT-1) currently enrolling[12]

Conclusions

- TSND-201 (methylone) directly enhances neurite outgrowth via NET, SERT, and DAT.
- Neurite outgrowth effects are modulated by mTor and BDNF/trkB signaling, further contributing to its neuroplastic effects.
- Rapid effects on neuroplasticity underscore its potential as a rapid, robust, and long-lasting pharmacotherapy for PTSD.

References

1. Warner-Schmidt et al., 2024, *Front Neurosci*, 18:1353131
2. Baumann et al., 2012, *Neuropsychopharmacology*, 37:1192
3. Poyatos et al., 2023, *Front Pharmacol,* 14:1122861
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8. Li et al., 2024, *Neuropharmacology*, 242:109787
9. Poyatos et al., 2021, *Biology,* 10(8):788
10. Poyatos et al., 2022, *Int J Mol Sci,* 23(23):14636
11. Jones et al., 2024, 62nd meeting of ACNP, Tampa, FL
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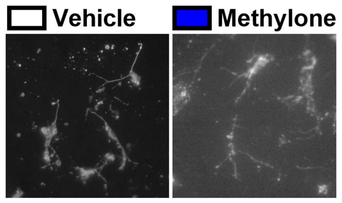
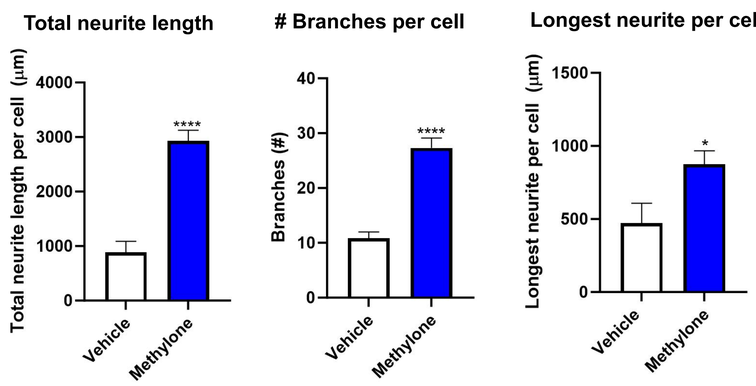
Disclosures

JW-S, MS, AJ, BM are full-time employees with equity in Transcend Therapeutics. BK has equity in Transcend Therapeutics.

Results

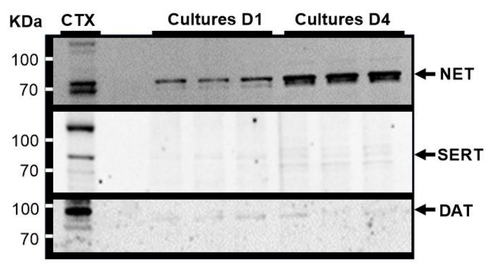
1. TSND-201 (methylone) increases neurite outgrowth

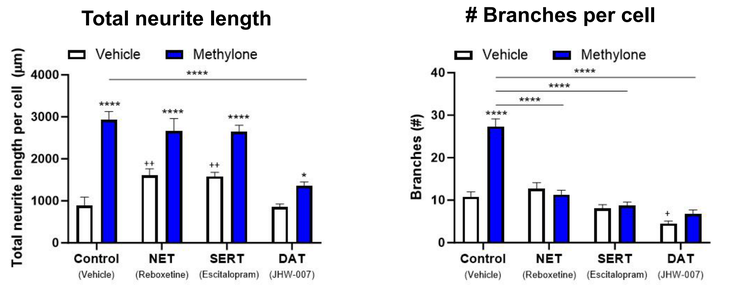




- Rat (E18) cortical cultures were stimulated with methylone (10µM) or vehicle on DIV1, fixed on DIV3-4, stained using β-tubulin III antibodies, visualized under 60X magnification, and analyzed using ImageJ software.
- Methylone significantly increased total neurite length per cell by increasing both the number of branches per cell and the length of the longest neurite per cell.

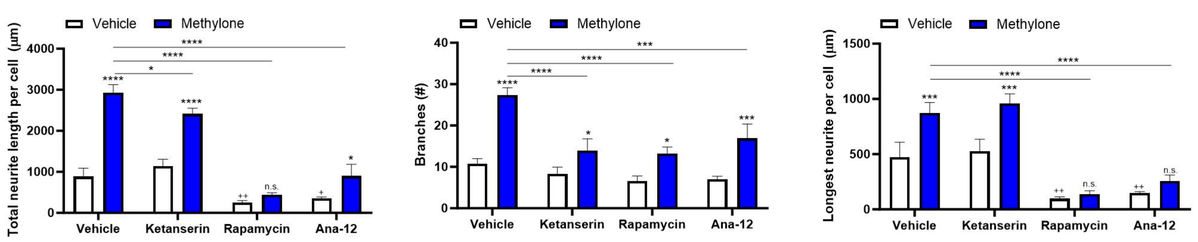
2. Neurite outgrowth effects are mediated by NET, SERT, DAT





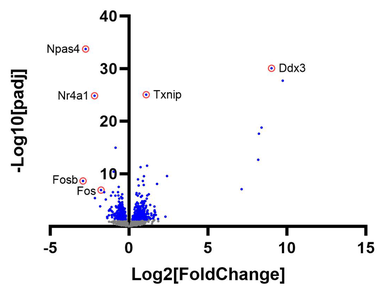
- NET, SERT, and DAT were detected by Western blotting. Cultures expressed all three transporters on DIV1 and DIV4.
- Pre-treatment with inhibitors of NET (reboxetine, 100nM), SERT (escitalopram oxalate, 10nM) and DAT (JHW-007, 100nM) blocked the effect of methylone on branching and blunted the effect of methylone on the length of the longest neurite (% change from vehicle = 85%, 35%, 44%, 33%, respectively).

3. Effects are also mediated by BDNF/trkB and mTor, not 5HT2A



- Pre-treatment with inhibitors of mTor (rapamycin, 10µM) or trkB (Ana-12, 10µM) blunted the effect of methylone on branching and blocked the effect of methylone on the length of the longest neurite.
- Blocking 5HT2A receptors with ketanserin (10nM) blunted the effect of methylone on branching and had no effect on the length of the longest neurite.

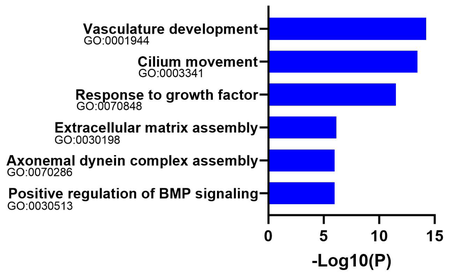
4. RNA-seq analysis supports rapid effects on neuroplasticity



Selected genes and function(s)

Ddx3	Neurite development
Txnip	Neuroprotection
Npas4	Regulates excitatory/inhibitory balance; synaptic plasticity
Nr4a1	Promotes neuroplasticity (IEG)
Fosb	Neuroplasticity; spine number
Fos	Regulates neuronal activity

Selected GO terms



- Cultures treated with methylone or vehicle for 24h were subjected to RNAseq analysis.
- Results confirm that genes and pathways that regulate axon outgrowth, neuronal growth, differentiation, and survival are induced by methylone treatment.