Preliminary characterization of TACT833, a novel MDMA-like benzofuran derivative

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1 Introduction

- MDMA is a proposed pharmacotherapy adjunct for the treatment of PTSD and other disorders.
- High or repeated doses of MDMA can cause long-term decreases in markers of serotonergic functioning.
- This may contribute to the subacute mood lowering and long-term loss of MDMA's therapeutic efficacy reported by nonmedical MDMA users.
- We sought to develop a novel benzofuran derivative that retained MDMA's therapeutic effects while lacking its long-term adverse effects on the serotonin system.

2 Methods

Drug Discrimination

- Adult male Sprague-Dawley rats were trained to discriminate MDMA (1.5 mg/kg, I.P., 15 min) under a FR 20 schedule of food reinforcement.
- Drug discrimination training and testing occurred in standard operant conditioning chambers, equipped with retractable levers and housed within sound-attenuating shells, controlled using Med-PC V software (Med Associates, St. Albans VT).
- In test sessions, stimulus substitution was assessed by reinforcing all responses. Sessions ended upon completion of the first FR 20 or after 20 min elapsed, whichever occurred first.
- TACT833 was administered in varying doses, IP, 30 min prior to test sessions.

Monoamine Release

- Crude synaptosomes were prepared from whole rat brain minus cerebellum and caudate.
- Synaptosomes were preloaded with 5 nM [3H]5-HT in KPB for 1 hour.
- Release assays were initiated by adding 850 µL of synaptosomes to test tubes containing 150 µL of KPB fortified with test drug. After 5 min, assays were terminated by rapid vacuum filtration.
- Retained radioactivity was quantified by liquid scintillation counting.

Monoamine Depletion

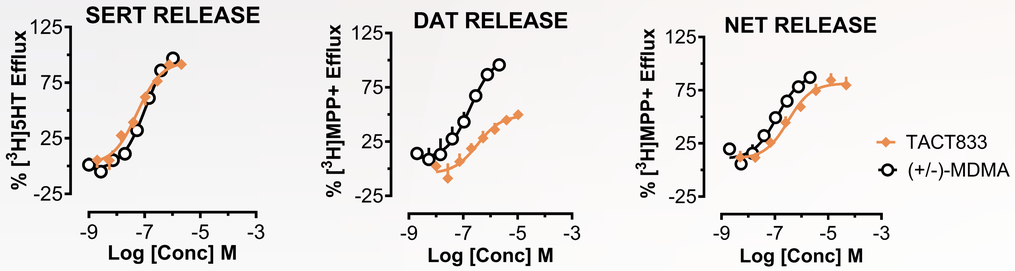
- Male Sprague-Dawley rats received repeated dose regimens of:
  - Saline (n=16)
  - 6.75 mg/kg IP TACT833 (n=16)
- Injections were every two hours for a total of three injections over six hours.
- Animals were sacrificed at two weeks after treatment and brains were assayed for 5-HT, DA, NE, and metabolites using HPLC with ultra-analytical dual electrode cell and reverse-phase C18 column.

Forced Swim Test (FST)

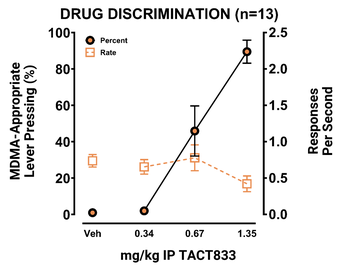
- Male Sprague-Dawley rats underwent three FST sessions, each 24-h apart: a 15-min habituation session and two 5-min test sessions.
- 30 min before the first 5-min test session, rats received treatments of:
  - Saline (n=13)
  - 1.35 mg/kg IP TACT833 (n=13)
  - 4.05 mg/kg IP TACT833 (n=13)
- Behavior was recorded on video and scored manually for immobility, swimming, and climbing plus diving time.

3 Results

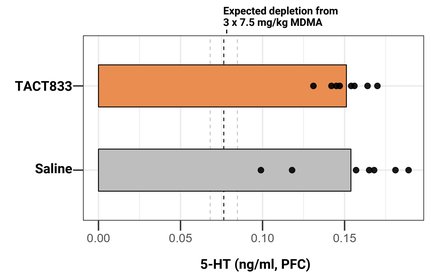
TACT833 is Full 5-HT & NE Releaser and Partial Dopamine Releaser



TACT833 substitutes for MDMA in Drug Discrimination

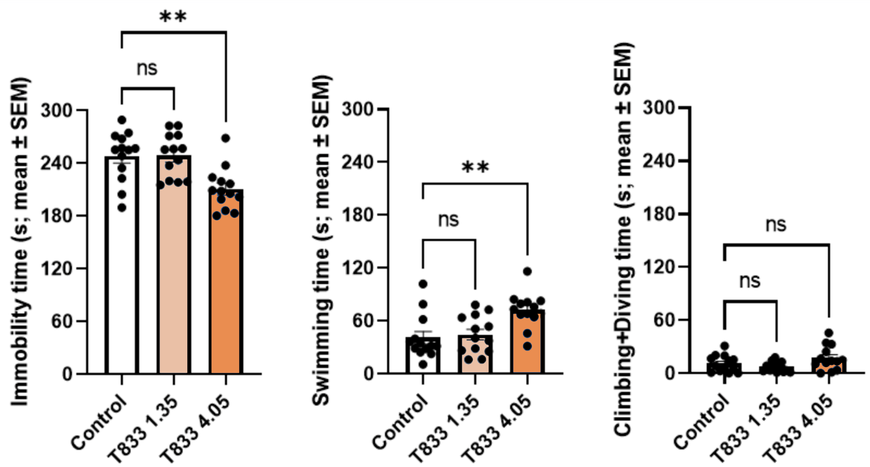


High, repeated TACT833 did not deplete monoamines at post two weeks



Above are representative results from broader assay panel in which 5-HT, DA, NE, DOPAC, 5-HIAA, HVA, 3MT were measured by HPLC in Prefrontal Cortex (PFC), Hippocampus, and Striatum and found to be unchanged at 2 weeks after TACT833 compared to saline control.

TACT833 showed an antidepressant-like effect in the Forced Swim Test (FST) at post-24 hours



(Not shown: both doses of TACT833 decreased immobility and increased swimming time and climbing plus diving time at 30 minutes after administration, although potential acute stimulant effects of TACT833 complicate interpretation.)

4 Conclusions

- Synaptosome release assays indicated that TACT833 is a full substrate-type releaser of 5-HT and NE and a partial releaser of DA, with EC_{50}s below 400 nM.
- TACT833 dose-dependently substituted for MDMA in the drug discrimination task
- Unlike MDMA, TACT833 did not produce long-term serotonin depletions after a repeated high-dose regimen.
- TACT833 had dose-dependent antidepressant-like effects in FST at post-24 hours.

5 Discussion

- TACT833 is a promising novel compound that may share the therapeutic effects of MDMA with minimal serotonin-lowering effects.
- TACT833 showed a post-24 hr FST effect as previously reported after BK-MDMA (Warner-Schmidt et al 2023), suggesting this may be a feature of at least some MDMA-like compounds.

Acknowledgements

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