

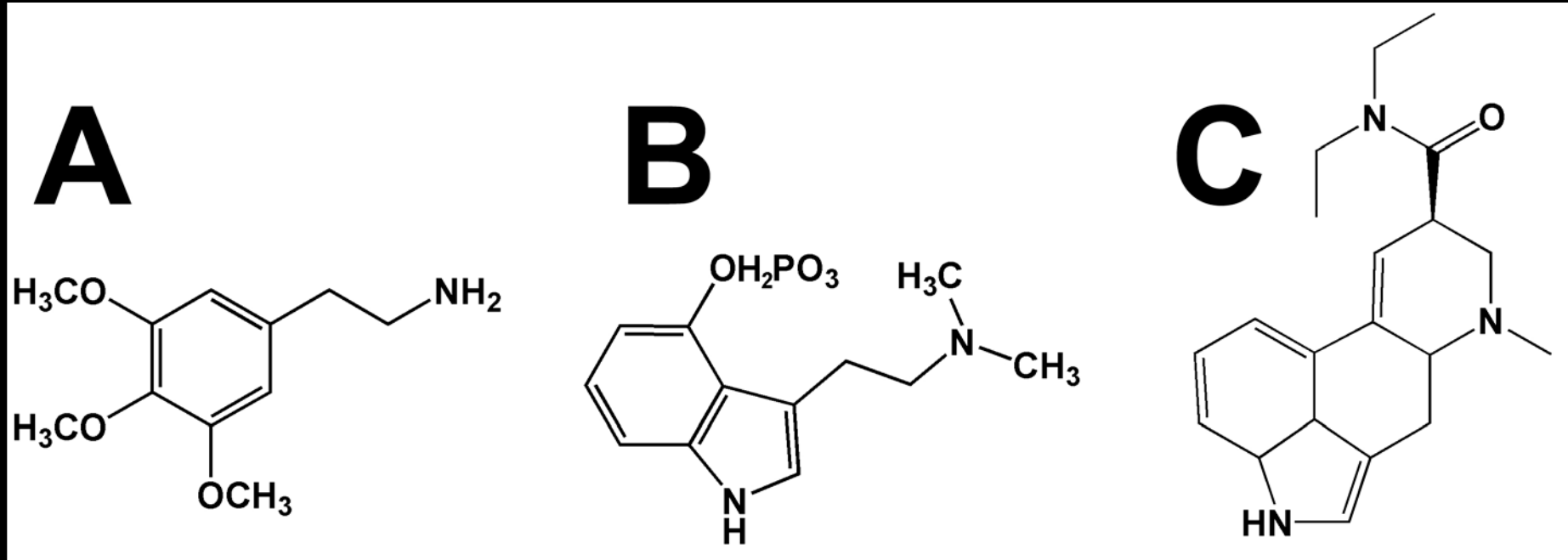
Tolerance Development to Hallucinogen-Elicited Head Twitch Behavior in Mice

William E. Fantegrossi, Ph.D.
University of Arkansas for Medical Sciences
Department of Pharmacology and Toxicology

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Definition of “hallucinogen”



- For pharmacologists, classical hallucinogens are drugs with chemical structures similar to mescaline (A), psilocybin (B), or LSD (C), with agonist affinity for 5-HT_{2A} receptors.

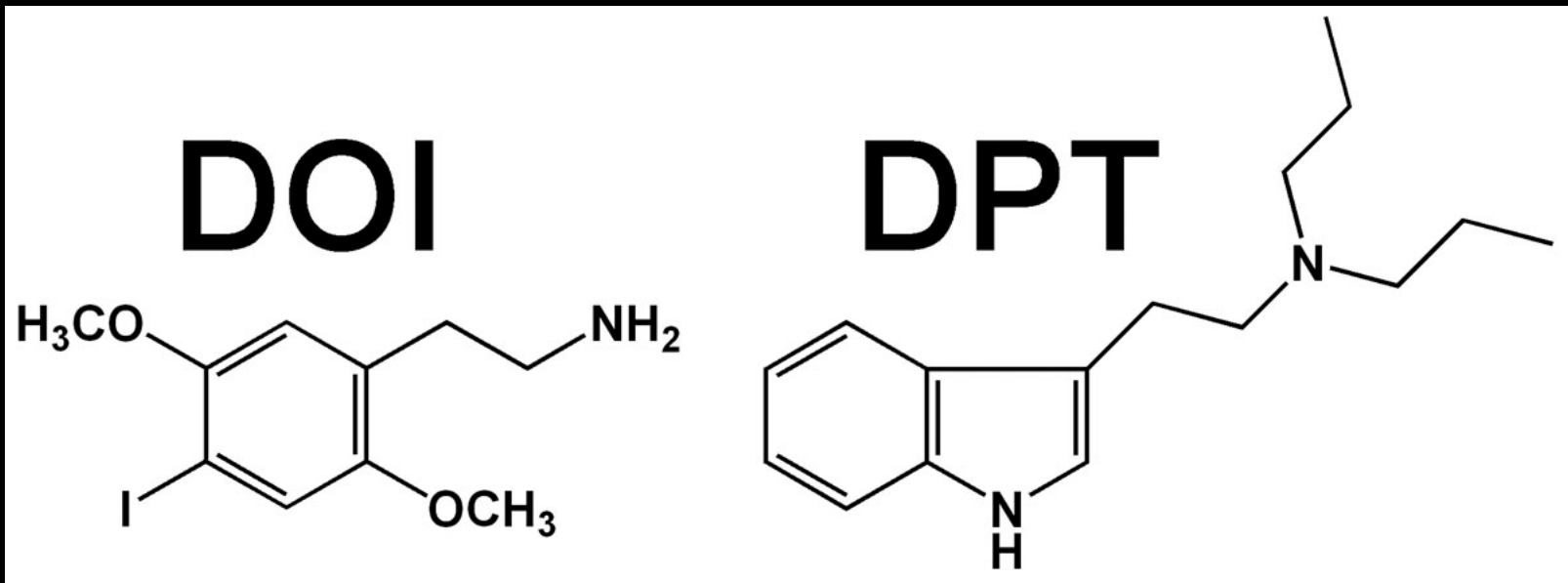
Behavioral model

- Drug-elicited head twitch behavior is a pharmacologically specific model for agonist efficacy at 5-HT_{2A} receptors in mice.
- Elicited by 5-HT precursors, releasers and selective 5-HT_{2A} agonists.
- Blunted by 5-HT depletion and selective 5-HT_{2A} antagonists.
- Use of model is growing with recent interest in 5-HT_{2A} as a target for novel therapeutics designed to treat depression and migraine headache.

Tolerance to hallucinogen effects

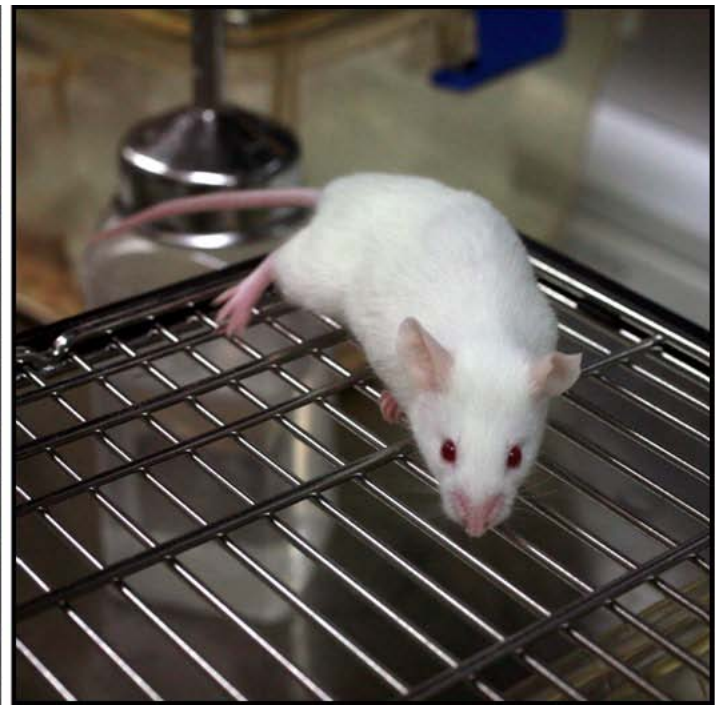
- One potential issue with therapeutics targeting 5-HT_{2A} is the fact that humans and lab animals rapidly develop tolerance to the behavioral and psychological effects of classical hallucinogens.
- Previous studies in this regard have used either LSD (an ergoline) or DOI (a phenethylamine).
- We were interested in comparing a tryptamine-based hallucinogen with DOI, as one of our chemist collaborators has synthesized a novel series of such compounds.

Phenethylamines vs. Tryptamines



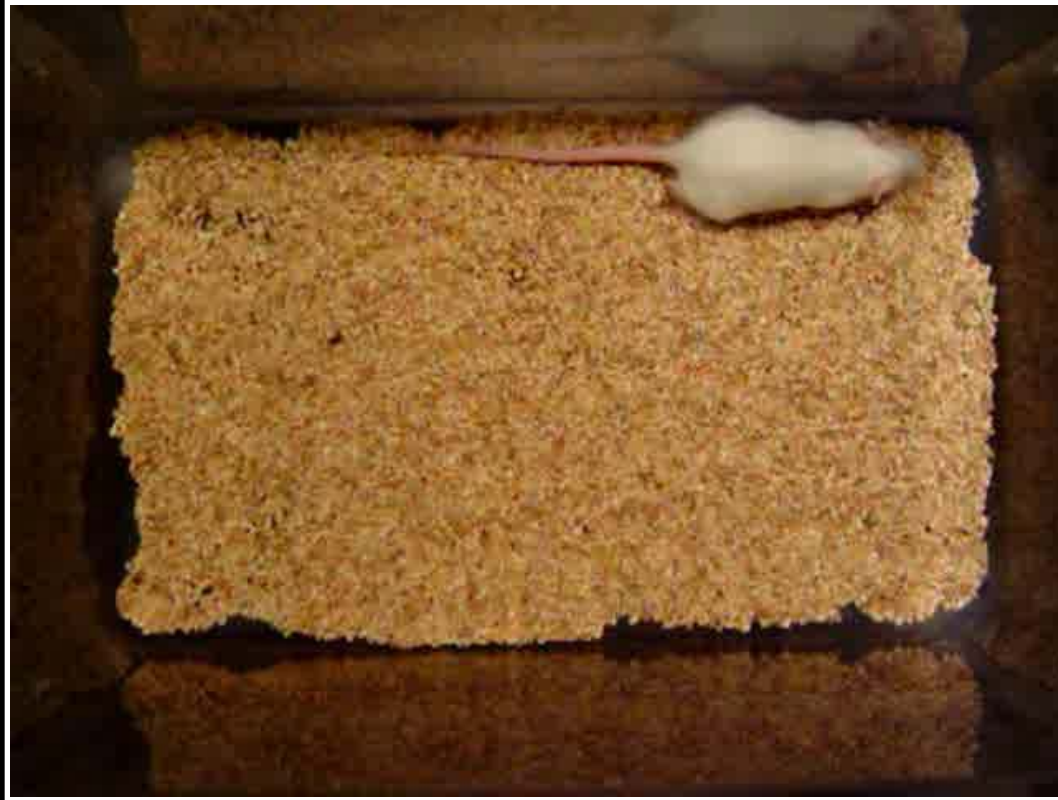
- Phenethylamines have highest affinity for 5-HT_{2C} and 5-HT_{2A} receptors.
- Tryptamines have highest affinity for 5-HT_{1A} and 5-HT_{2A} receptors.

Methods



- Adult male Swiss Webster mice
- All drugs dissolved in saline, all injections administered IP

Methods



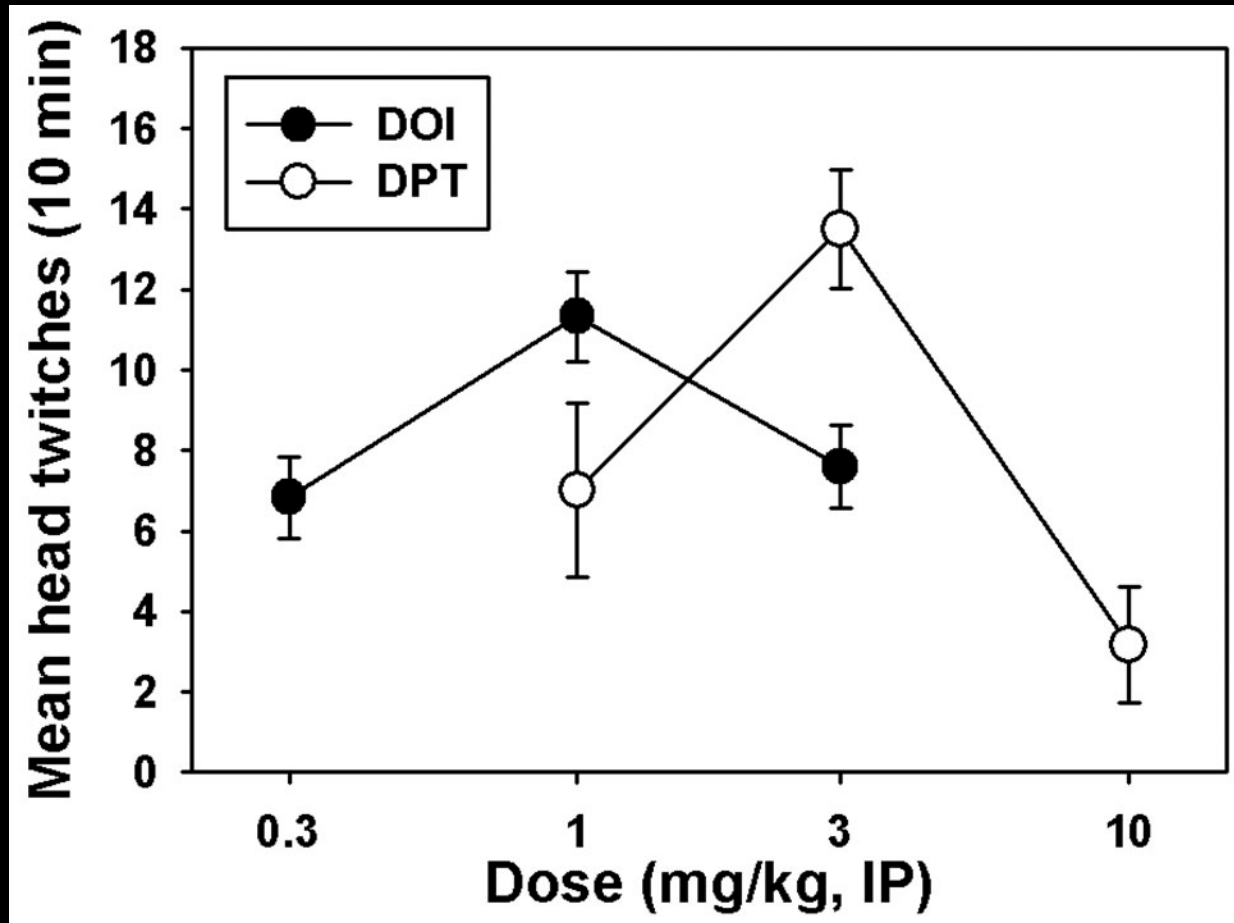
- Rapid, rotational jerk of the head.
- Not contiguous with species typical grooming or scratching behaviors.

Methods



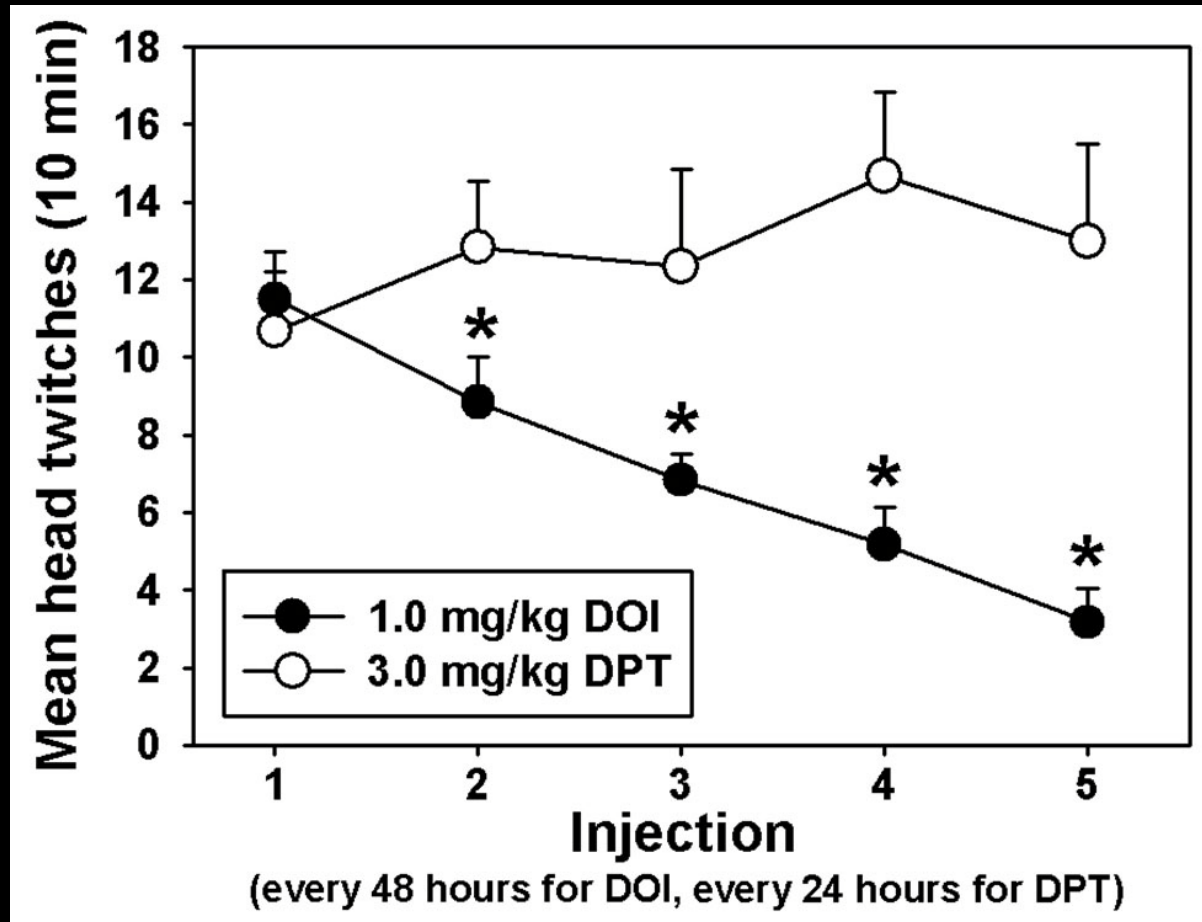
- **Sessions scored by 2 trained observers blind to treatment conditions (inter-rater reliability > 95%)**

Results



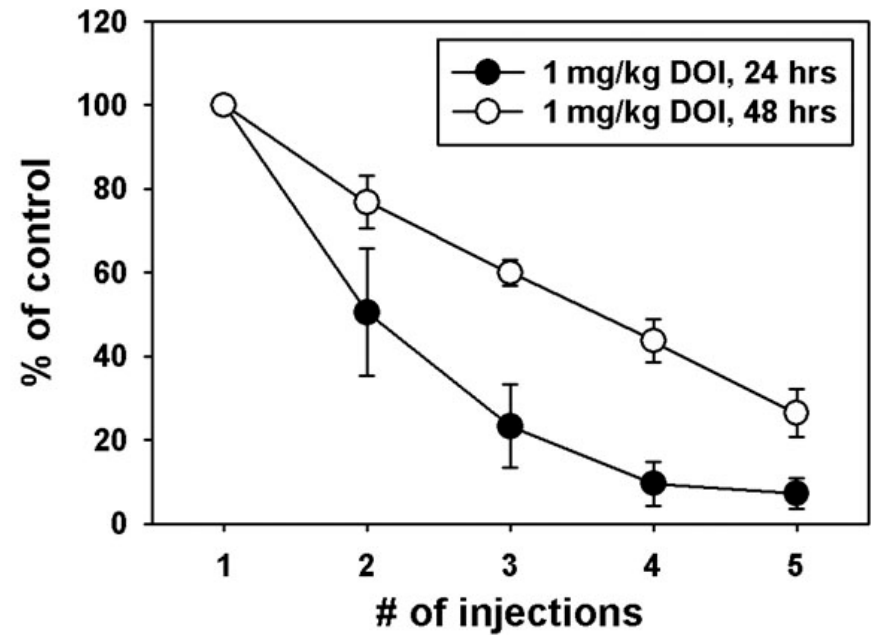
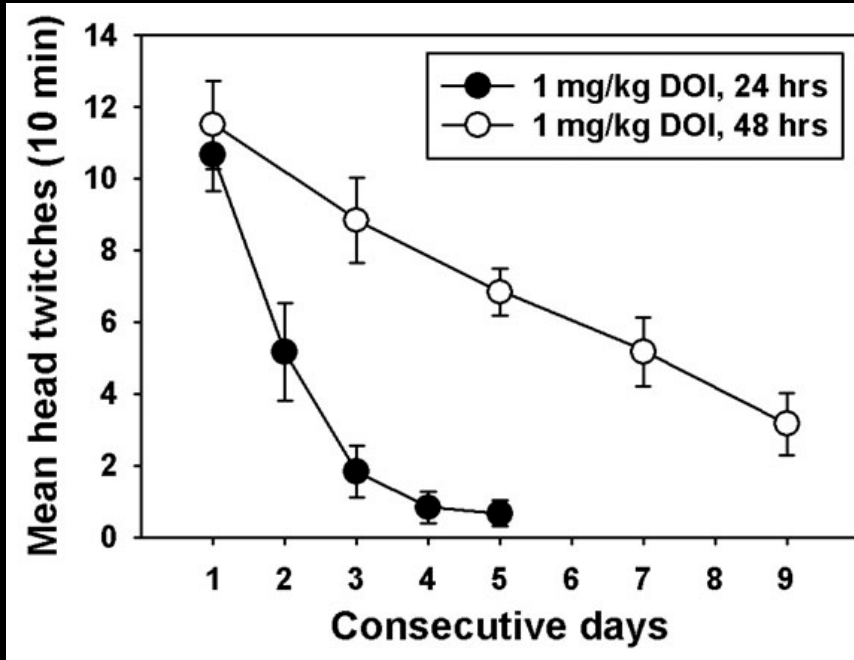
- DOI is more potent, but both drugs elicit the same maximal effect.

Results



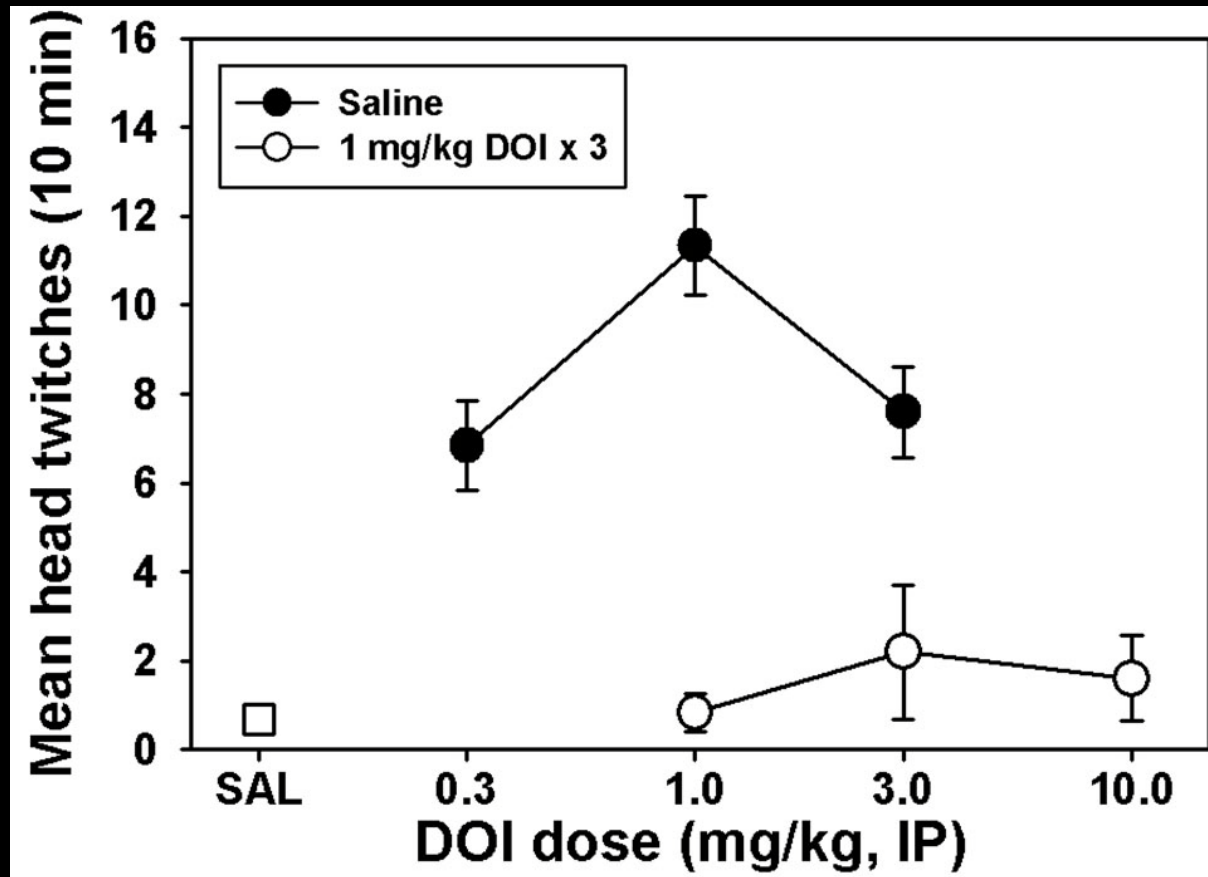
- Decreased effectiveness of DOI, but no change in DPT response, even with more frequent dosing.

Results



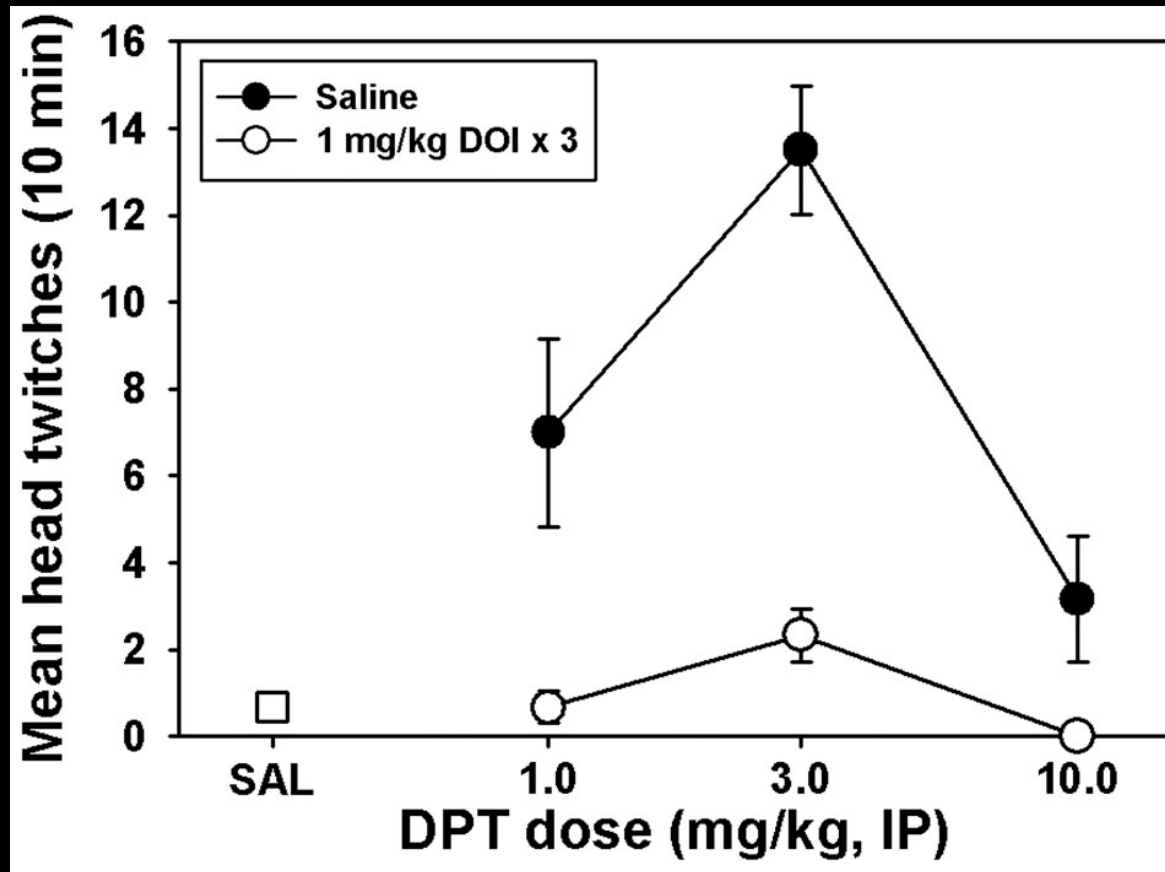
- Tolerance to DOI-elicited head twitch behavior develops more rapidly if the drug is administered more frequently.

Results



- Tolerance to DOI-elicited head twitches is functionally insurmountable (convulsions at 30.0 mg/kg).

Results



- Mice made tolerant to DOI-elicited twitch behavior are also cross tolerant to DPT.

Conclusions

- Tolerance to DPT-elicited head twitches does not develop with repeated treatment, but cross-tolerance is evident in mice previously treated with DOI.
- Potential mechanisms underlying this apparent discrepancy (role of 5-HT_{1A} receptors, duration of drug action, etc.) are currently being explored.



Acknowledgements

