Acute tetrabenazine (TBZ) challenge as a translational approach to study novel antidepressants

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Introduction

Tetrabenazine (Xenazine®; TBZ) is an FDA drug approved treatment for hyperkinetic movement disorders such as Huntington's Chorea. As a reversible inhibitor of the VMAT2 protein, TBZ produces a temporary and reversible depletion of the monoamines 5-HT, DA and NA in forebrain and limbic CNS regions (frontal cortex, hippocampus, striatum), through a disruption of vesicular storage. As a likely consequence, depression is a recognised side-effect of TBZ in humans, and the behavioural changes reported in rodents characteristic of depression relevant endophenotypes such as anergia, amotivation, inattention, negative bias and anxiety (e.g. Nunes et al., 2013; Stuart et al., 2017). In the present studies we have characterized the effect of TBZ (0.3-3mg/kg) on measures of monoamine neurochemistry, motivation (progressive ratio (PR), food choice tests), cognition (5-choice serial reaction time task (5-CSRTT)) and locomotor endurance (running wheel) in adult, male, Long-Evans rats. The effect of the NA/DA reuptake inhibitor bupropion (BUP; 10-20 mg/kg), and the SSRI citalopram (CIT; 1-10 mg/kg) was investigated against the TBZ-induced deficits.

Methods

Animals: Adult, male Long Evans rats were used in all studies except in the wheel running expt. which used adult, male Sprague-Dawley rats (source: Charles River, St. Constant, Quebec, Canada).

Treatments: All drugs administered by the IP route. BUP and CIT were administered 30min prior to TBZ or vehicle. Doses expressed as base.

Neurochemistry: Test subjects (N=7/group), dosed with either vehicle or TBZ (0.3-3 mg/kg IP) and sacrificed at either 1.5, 3, and 72 h post dose. Blood also collected by cardiac puncture for measurement of plasma TBZ/HTBZ levels. The frontal cortex, hippocampus, and striatum each dissected and analysed for monoamine content (AB Sciex API6500 QTRAP LC-MS/MS system).

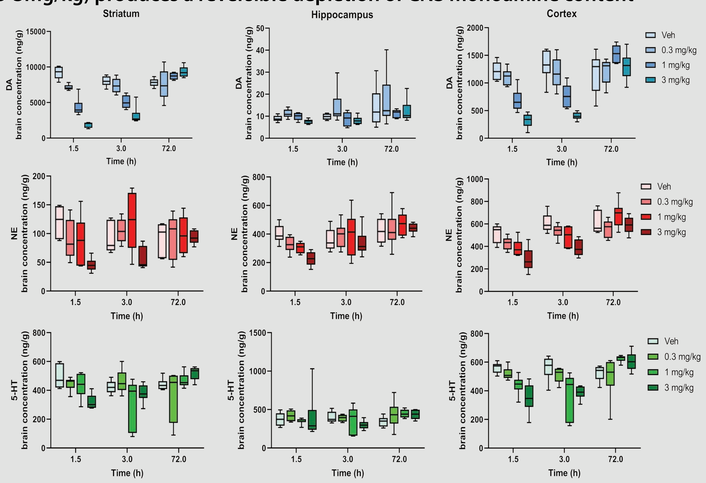
Progressive ratio: Test subjects trained to respond for food under a progressive ratio (PR) schedule according to the progression 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, etc. A rat was assumed to have reached the break point if it failed to receive a reward for 20 min. Drug testing began once rats performed at asymptote.

5-choice serial reaction time task: Test subjects trained to asymptotic performance in the 5-CSRTT to a final stimulus duration (SD) of 0.75s, 5s inter-trial interval (ITI), 5s limited hold (LH), 100 trials per session. Target performance levels under these conditions were in the range of >80% accuracy, <20% omissions. Once performance stable, test challenge and drug testing began. Two challenge approaches were taken, (A) a 250 trials version, and (B) a sITI (2-5s) schedule (see Higgins and Silenieks, 2017).

Running wheel: Test subjects were acclimated and trained until asymptotic spontaneous activity in running wheels (Lafayette Instruments) is achieved. Following, rats were administered TBZ and immediately placed into running wheels for 6h. (A) Dose finding and characterization of TBZ (0.3, 1, 3mg/kg, IP) and (B) Reversal of TBZ deficits with BUP (20mg/kg, IP, 30min ptt) and TBZ (1.5mg/kg, IP).

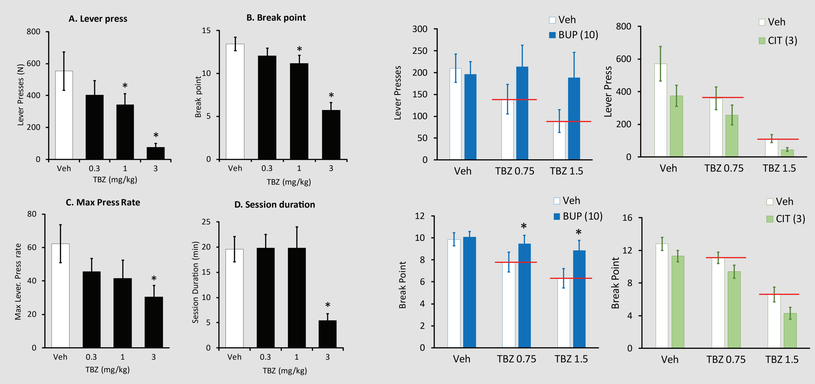
Results

TBZ (0.3-3mg/kg) produces a reversible depletion of CNS monoamine content



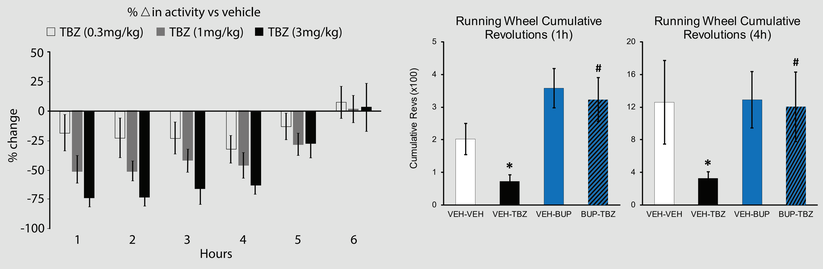
TBZ (0.3-3 mg/kg IP) produced a dose-related decrease in monoamine content 1.5 and 3h post injection. These timepoints correspond to when behavioural testing was conducted (except see running wheel). By 72h all monoamine levels had returned to baseline levels.

TBZ (0.3-3 mg/kg) reduces motivation: Attenuation by BUP, not CIT



TBZ (0.3-3 mg/kg IP) produced a dose related decrease in break point, rate of lever press and session duration in a progressive ratio task. BUP attenuated the TBZ-induced decline. CIT no effect.
* P<0.05 vs. vehicle or corresponding TBZ dose/vehicle group.

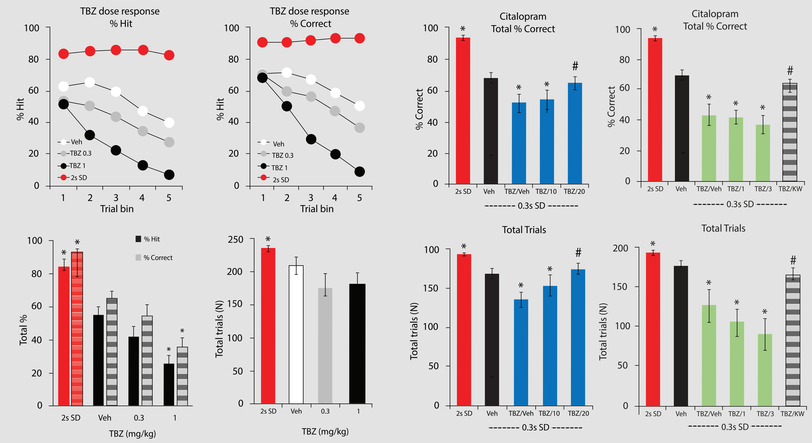
TBZ (0.3-3 mg/kg) reduces wheel running: Attenuation by BUP



A. TBZ (0.3-3 mg/kg IP) produced a dose related transient reduction in running wheel activity. B. BUP (20 mg/kg) was able to reverse activity deficits from TBZ (1.5 mg/kg) (N=10). BUP alone produced a small increase in running wheel activity (N=16 , * P<0.05 vs VEH+VEH, # P<0.05 vs VEH+TBZ).

Results

TBZ (0.3-1mg/kg) reduces sustained attention: Attenuation by BUP, not CIT



TBZ (0.3-1 mg/kg IP) produced a dose and trial dependent decrease in % correct and % hit, i.e with increasing trial number TBZ impairment becomes more pronounced. Total trial # also reduced. When rats tested under longer SD (2s), animals stay on task longer, suggesting any decline in vehicle treated controls is unrelated to satiation. Pretreatment with BUP (but not CIT) attenuates the TBZ (0.75 mg/kg) decline measured both as % correct and total trials completed. * P<0.05 vs. Veh/0.3s SD; # P<0.05 vs. TBZ/Veh 0.3s SD.

Summary

- TBZ (0.3-3 mg/kg IP) produces a dose-related, titratable, approach to transiently decrease forebrain DA, NE, 5-HT levels.
- Reversibility of TBZ effect enables repeated measures designs.
- Plasma exposure of TBZ (1mg/kg) equivalent to clinical Xenazine exposure (i.e 4-8 ng/ml; see Mehvar et al, 1987).
- TBZ decrease in motivated behaviour attenuated by BUP not CIT.
- TBZ decrease in sustained attention (cognitive fatigue?) is attenuated by BUP not CIP. A2a antagonist KW-6002 also +ve.
- The transient nature of TBZ effect limits running wheel measurement to first 4h. BUP only produced a partial attenuation possibly related to limited plasma exposure >2h post dose.
- The TBZ model may represent a novel translational approach to study drug effects against depression related endophenotypes both in rodent and human.

References

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