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A Drug for All Ages: Levetiracetam Enhances Attention in Both Young and Aged Rats

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INTRODUCTION

Levetiracetam (LEV) is primary treatment for seizure disorders [1]. LEV is a close structural analog of piracetam, a nootropic. In addition to the epilepsies, LEV may be of benefit to the treatment of some cognitive disorders such as MCI, early Alzheimer's disease, and Autism Spectrum Disorder although definitive evidence is limited unlike its well-defined anti-seizure property [1].

The present study has evolved from an earlier study that reported mild attentional improvements in rats trained to a 5-CSRTT following LEV pretreatment [2]. The present study utilized male, Long-Evans rats at two distinct life stages, young (Y: 3-9 months) and aged (AG: >18 months). LEV (10-60 mg/kg) was tested under multiple task conditions of the 5-CSRTT. Equivalent doses of LEV were also evaluated in an amygdala kindling study for reference purpose.

METHODS

Animals and Housing
Long Evans (5-CSRTT) rats, (source: Charles River, St. Constant, QC, Canada) served as test subjects for the 5-choice studies. All rats were singly housed and food restricted. Male, Wistar rats were utilized for the amygdala kindling experiment All in-life studies were approved by an Institutional animal care committee according to guidelines established by the CCAC.

Drugs
Levetiracetam was prepared in 5% tween 80 in saline and dosed by the IP route, 60min before onset of the test session.

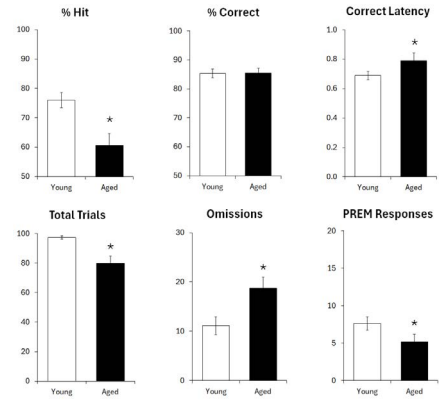
5-choice procedure (see Higgins and Silenieks, 2017)
Test subjects trained to asymptotic performance in the 5-CSRTT to a final stimulus duration (SD) of 0.75s, 5s inter-trial interval (ITI), 5s limited hold (LH), 100 trials per session. Target performance levels under these conditions were in the range of >80% accuracy, <20% omissions. Once performance stable, test challenge and drug testing began.

Subjects tested under three challenge conditions:-
(A) Standard task conditions (0.75s SD; 5s ITI; 100 trials)
(B) Short variable ITI (2-5s) schedule (0.3s SD; 2, 3.5, 5s ITI; 40 trials per ITI, i.e. 120 trials total).
(C) Extended 250 trials schedule (0.3s SD, 5s ITI, 5 x 50 trial bins, i.e. 250 trials total.

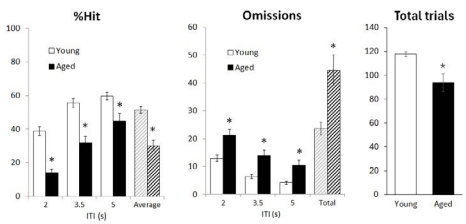
Amygdala kindling procedure (see Silenieks et al, 2019)
Test subjects were surgically implanted with a bipolar electrode aimed at the right basolateral amygdala. Following a 1-week recovery period, kindling training commenced. The kindling stimulus was a 1s train of 60 Hz biphasic square-wave pulses at 400 □A. Kindling stimulus delivered once a day, 5 days/week, until a criterion of 30 stage 4/5 seizures was reached. At this point drug testing began by a repeated measures design.

RESULTS – Effect of age on 5-CSRTT performance

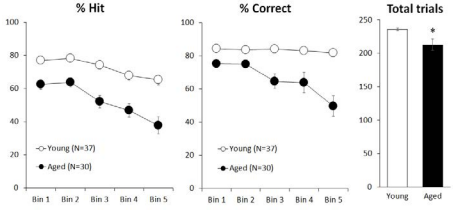
Standard task conditions



sITI task condition



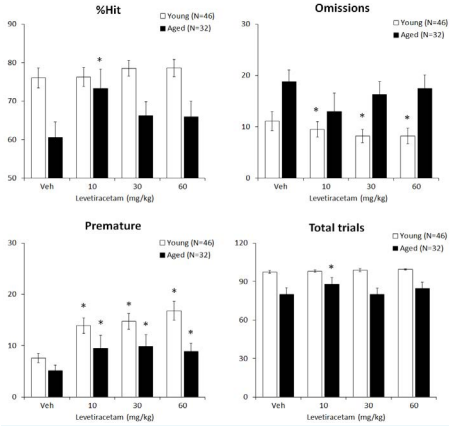
Extended trials task condition



For each task condition, data presented as means±SEM for Y and AG rats. For 250 trials, each Bin = 50 trials. * P<0.05 vs. vehicle control from the relevant age group.

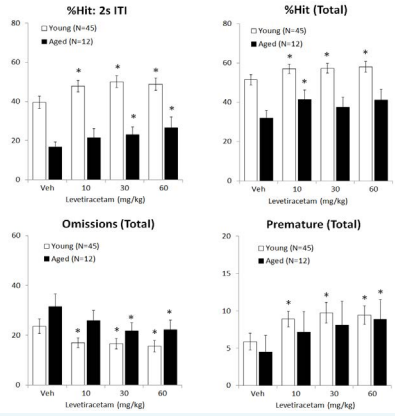
RESULTS – Effect of LEV on age related 5-CSRTT performance

Standard task conditions



Data presented as means±SEM for Y and AG rats tested under standard conditions in the 5-CSRTT. * P<0.05 vs. vehicle control from the relevant age group.

sITI task condition



Data presented as means±SEM for Y and AG rats tested under sITI conditions in the 5-CSRTT. Total % Hit refers to the mean % Hit for each animal across each ITI. * P<0.05 vs. vehicle control from the relevant age group.

RESULTS – Effect of LEV on amygdala kindling model

Compounds	Racine score	ADD (s)	[Plasma]
Vehicle	4.8±0.2	94.0±6.8	-
LEV (30 mg/kg IP)	3.0±0.9	62.7±23.9	-
LEV (60 mg/kg IP)	1.3±0.7 *	24.2±7.7 *	11µg/ml

Data presented as means±SEM for male Wistar rats (~ 12 months age). * P<0.05 vs. vehicle control. Plasma levels were measured 1h post dose.

CONCLUSIONS

- **AG rats show some performance deficits in the 5-CSRTT relative to Y rats. Under standard conditions these deficits are seen by higher omissions, slower response speed. Accuracy measured as % correct is relatively unaffected, but factoring omissions into the accuracy measure (i.e. % Hit) reveals an age deficit.**
- **Introducing challenge conditions such as sITI and extended 250 trials further emphasise age related performance deficits on measures such as % hit.**
- **LEV (10-60 mg/kg) was evaluated on performance of Y and AG rats under standard and sITI test condition.**
- **In Y rats, LEV produced a modest increase in response speed (i.e. faster), increased PREM responses, lower omissions. In the sITI schedule, improvement in % hit was reliably detected, although under standard conditions this effect was not evident.**
- **In AG rats, LEV similarly increased PREM responses, reduced omissions and produced some improvement in % hit.**
- **Effective doses of LEV on 5-CSRTT overlapped with doses effective in a rat kindling model and at plasma exposures of 5-11ug/ml which is in the clinical range of LEV used in treatment of seizures [1].**
- **These data support a potential for SV2A modulators as treatments for some clinical conditions associated with cognitive impairment [1].**

REFERENCES

1. Loscher W et al (2016) Synaptic Vesicle Glycoprotein 2A Ligands in the Treatment of Epilepsy and Beyond. CNS Drugs 30: 1055-1077.
2. Higgins GE et al (2010) Comparative study of five antiepileptic drugs on a translational cognitive measure in the rat: relationship to antiepileptic property. Psychopharmacol. 207: 513-527.