MAO-A inhibitor clorgyline administered in chronically sleep deprived mice fails to protect neuronal health and slow Alzheimer's pathology progression

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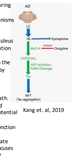
Introduction

- Alzheimer's Disease (AD) is well-known as a disease featuring memory loss and confusion, typically in older patients
- Chronic sleep disruption is a risk factor for AD, yet mechanisms underlying this are unknown
- CSD and AD impact noradrenergic neurons in the locus coeruleus. Phosphorylation of the protein tau in locus coeruleus neurons (LCn) is one of the first sites of AD neurodegeneration and injury.
- Noradrenaline (NA), a catecholamine neurotransmitter in the same family as serotonin and epinephrine, is metabolized by monoamine oxidase-A (MAO-A) into DOPEGAL, which then activates AEP to cleave tau at N368.
- This process can promote aggregation and continued phosphorylation of tau, eventually leading to neuronal death.
- Therefore, inhibiting the breakdown of NA by MAO-A and slowing the production of DOPEGAL in CSD mice has the potential to slow neural injury and AD progression.
- Clorgyline is a drug that pharmacologically inhibits the function of MAO-A, therefore inhibiting NA breakdown.
- Studies focusing on clorgyline are limited, and many to-date have focused on clorgyline in other functions. This study focuses on the effects of clorgyline on LC morphology and neuronal health.



Kang et. al, 2019

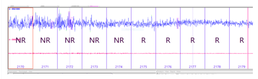
Research Question

Can monoamine oxidase A (MAO-A) inhibitor clorgyline slow the progression of tau aggregation in chronically sleep deprived mice?

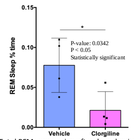
Methods

- Mice were randomized to daily vehicle or clorgyline therapies, given at 2mg/kg subcutaneously
- All mice were exposed to CSD from 10AM-4PM for two weeks
- CSD consisted of an enriched environment that was constantly changed to ensure mice were alert
- EEG and EMG recordings were taken 3 times throughout CSD and scored using SleepSign
- Mice were deeply anesthetized and perfused, and brains sectioned
- Immunohistochemistry staining was done for Cfos+ and AEP Tau
- Imaging was done on immuno-stained brain slices on a Confocal microscope, then ImageJ was used to discern differences between groups
- Stereology was done to count LC neurons
- Unpaired t-tests and linear regressions were run using Prism

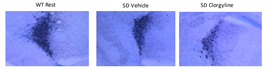
Results



Transition from NREM to REM sleep in vehicle mouse



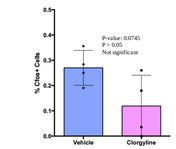
Total REM suppression after sleep deprivation



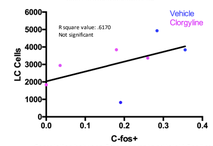
Locus coeruleus in rested, vehicle SD, and clorgyline SD mice

B6 Clorgyline	Count	B6 Vehicle	Count
	4904	3367.58	4903	4934.56
	4906	3840.64	4909	824.48
	4908	2942.98	4911	3838.94
	4910	1835.84		
Average		2996.76	Average	3199.326667

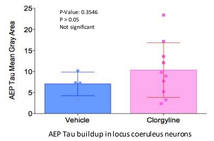
Total LC cell counts after TH stereology staining



Cfos+ stained cells after SD



Correlation between Cfos+ content and total LC cell count



AEP Tau buildup in locus coeruleus neurons

Conclusions

- Clorgyline significantly suppressed REM sleep, suggesting the levels were sufficient to have effects in the brain
- CSD induced LC dysmorphogenesis in both groups
- Cfos+ cell counts were higher in vehicle mice, suggesting more LC activation in response to wakefulness
- There was no significant difference in total LC cell counts between the two groups, indicating that the drug did not protect from neuronal damage
- There appears to be higher AEP Tau content in clorgyline cells compared vehicle, suggesting greater CSD injury

Future Directions

- Larger sample sizes are needed to understand clorgyline's impacts on brain morphology
- When adjusting the study, a fully rested control group for both conditions should be added for comparison
- Discussion of norepinephrine neurotoxicity is important to evaluate potential detrimental side effects of clorgyline

References

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Acknowledgements

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