CHRONIC MEMANTINE TREATMENT RESTORES PASSIVE AVOIDANCE BUT NOT SPATIAL MEMORY FOLLOWING OLFACTORY BULBECTOMY

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INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the elderly population, and has been characterized by elevated intraneuronal Aß peptide accumulation - one of the earliest pathological events leading to neurodegeneration. However, in the early stages of AD, Aß deposition is poorly correlated with the degree of cognitive decline, suggesting that additional factors other than aging and genetics might be involved in early AD progression. Elevated levels of extracellular glutamate and potentially an enhanced stimulation of glutamate N-methyl-D-aspartate (NMDA) receptors are associated with neuroinflammation and the neurobiology of both AD and depression- serious neuropsychiatric conditions, which can no longer be examined as two completely separate entities, especially in the elderly population. Several reports suggest that depression is not just a side effect of AD, but rather a possible prodrome, which might become a predictive value for AD development. Memantine (MEM), an NMDA antagonist, has been clinically used for the treatment of moderate-to-severe AD, and has been shown to improve spatial learning in AD transgenic animals. To investigate a therapeutic effect of chronic administration of MEM in a model of cognitive decline, we chose olfactory bulbectomized (OBX) rat model. Ablation of the olfactory bulbs in the rodents induces pathological phenotype of the AD and MDD patients, suggesting that OBX animal model possess both face and predictive validity a and therefore, an ideal model for our investigation.

AIM

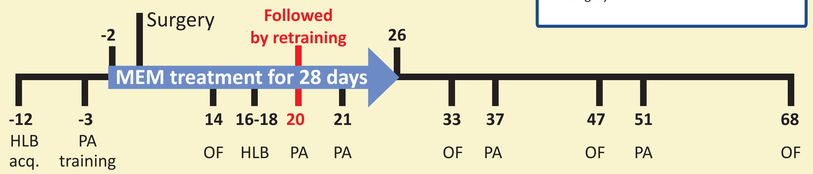
(i) To examine whether memantine would be able to rescue cognitive deficits and ameliorate the depressive-like symptoms mediated by OBX in a time-dependent manner

(ii) To observe the duration effect of chronic memantine administration after treatment cessation

MATERIALS AND METHODS

Experiment 1, MEM starting 14 days post OBX surgery.

Experiment 2, MEM starting 2 days prior OBX surgery.

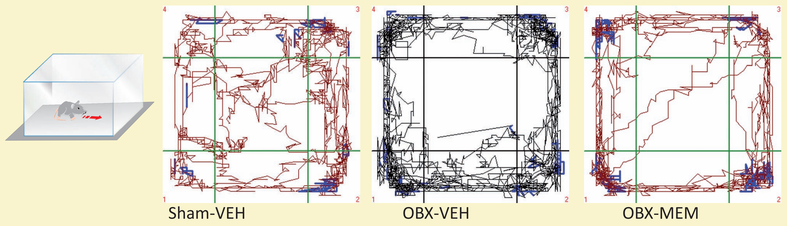


OBX surgery
Removal of olfactory bulbs→Long-lasting neurochemical, behavioral, and cognitive changes resembling those of AD/depressed patients.

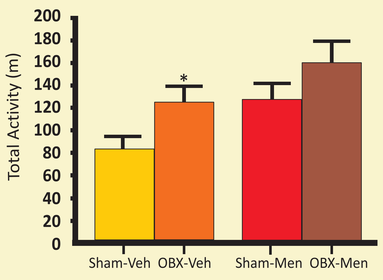
Drug administration
MEM at 20 mg/kg (Lundbeck, Denemark) or water, were orally administered for 28
Experiment 1- starting 2 days prior to OBX surgery
Experiment 2- starting 14 days after the surgery

Total activity in the Open Field (OF)

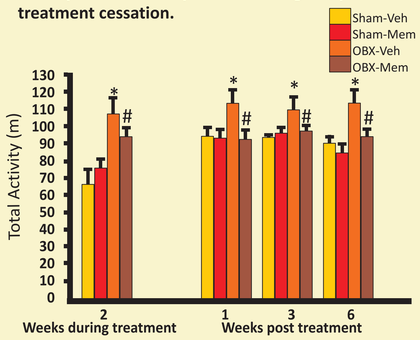
Locomotor patterns in the open field of an OBX, a sham-operated, and an OBX rat treated with MEM



Chronic MEM treatment starting 14 days post OBX surgery, amplified activity levels in the open field in both sham and OBX animals.

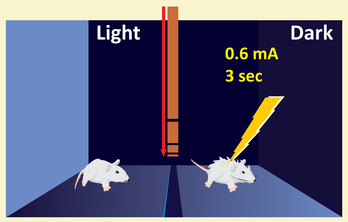


Chronic MEM treatment starting 2 days prior OBX surgery, normalized OBX mediated increased activity levels in the open field during and post treatment cessation.

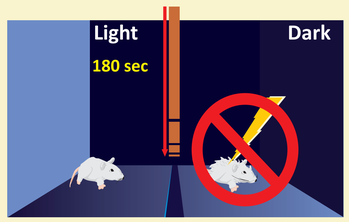


Fear memory in step-through Passive Avoidance (PA)

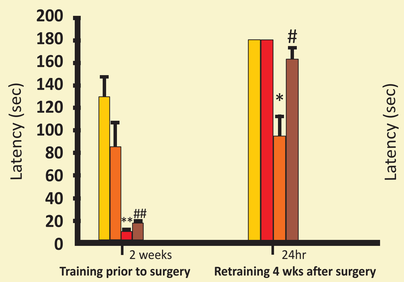
Training



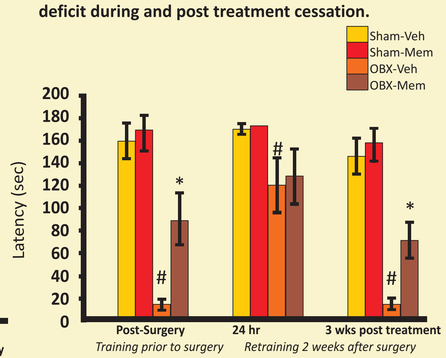
Test



Chronic MEM treatment starting 14 days post OBX surgery rescued OBX- induced fear memory impairment

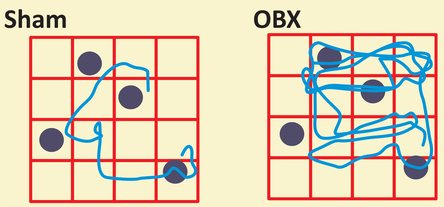


Chronic MEM treatment starting 2 days prior to OBX surgery rescued OBX- induced fear memory deficit during and post treatment cessation.



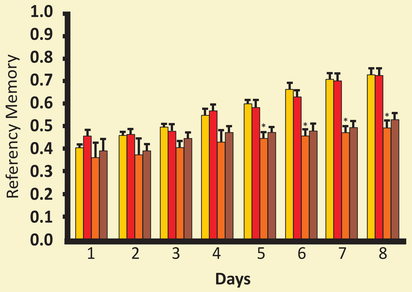
Spatial memory acquisiton and memory in Holeboard (HLB)

Typical tracking traces from sham and OBX animals during spatial memory task

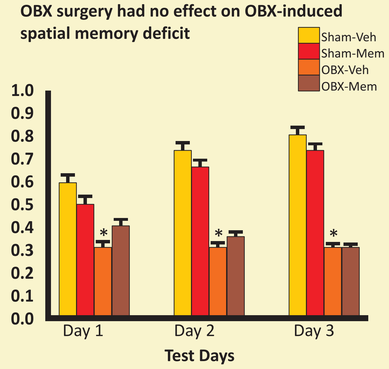


Habituation : 3 days
Acquisition : 4 trials per day, 8 days
Retention : 3 days

Chronic MEM treatment starting 14 days post OBX surgery had no effect on OBX-induced spatial memory acquisition deficit



Disrupted spatial memory following OBX. Chronic MEM treatment starting 2 days prior to OBX surgery had no effect on OBX-induced spatial memory deficit



CONCLUSION

- **MEM has long-lasting memory-enhancing and antidepressant properties after early administration. However, MEM seems to loose its efficacy when administered well into the development of the OBX-induced behavioral and cognitive abnormalities.**
- **Current data suggest that MEM treatment starting in the early phases of the cognitive decline maybe more beneficial, especially when combined with other anti-dementia treatment, and therefore, should be further investigated inclinical trials.**

No potential conflict of interest

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