A multicomponent medication enhances cognitive function in vivo

K. Roeska*, S. Wagner, E. Andriambeloson, Y. Burmeister, B. Seilheimer*
Neurofit SAS, Illkirch, France, *Biologische Heilmittel Heel GmbH, Baden Baden, Germany

INTRODUCTION

A characteristic feature of patients with dementia is neuronal degeneration of hippocampal cholinergic neurons leading to a marked decline in cognitive function. This loss of cholinergic neurons might result in a deficiency of acetylcholine in specific brain regions that mediate learning and memory. Acetylcholine inhibitors such as Donepezil and Galantamine are approved drugs with noticeable effects on the symptoms of dementia. However, strong side-effects and low efficacy limit their clinical benefit. To date a disease modifying drug is not available.

He-300 is a multi-component medication consisting of several different natural sources. Thus the efficacy arises from different biochemical levels. It was already observed that HE-300 changes gene expression in AD specific genes, affects synaptic plasticity, neuronal outgrowth and APP processing. These data suggest that HE-300 exhibits potential to support cognitive function by targeting several cellular networks. The treatment with such a multicomponent/multi-target drug depicts a new and innovative approach for a beneficial treatment of this complex and chronic disease.

OBJECTIVE

In the present study, we assessed the effect of HE-300, a multicomponent medication derived from natural sources on cognitive function using two different in vivo animal models. HE-300 was tested in

(1) the T-maze continuous alternation task in mice with scopolamine-induced learning deficits.
(2) the novel object recognition test in naive rats, investigating the natural forgetting behaviour.

MATERIALS & METHODS

T-maze assay: The percentage of alternation of 14 free-choice trials was determined for each mouse and was used as an index of working memory performance. This percentage was defined as entry in a different arm of the T-maze over successive trials. Drug induced reversion was calculated by considering the saline/vehicle group as 100% and scopolamine/vehicle group as 0%. Mice were treated with 10 ml/kg Scopolamine. HE-300 was administrated acutely or during 3 consecutive days prior to the trail. The last treatment was given 40 min before the test. Donepezil was given at 0.3mg/kg 20 min before the trial. All drugs were given intraperitoneally.

Novel object recognition: Each animal was exposed to this situation for 10 min. Time spent exploring each of the 2 objects during the retention trial was recorded. Recognition memory was evaluated using a recognition index (RI) that corresponds to the proportion (%) of time spent on the retention trial investigating novel object with respect to total time spent investigating familiar object and new object. RI was calculated as follow: RI = tNO/(tFO+ tNO) x 100, where t denotes time. Recognition index was also expressed as the number of visit (contacts) to the novel object in % and was calculated as follow: RI = nNO/(nFA + nNO) x 100, where n denotes number of contacts.

Statistical analysis: Statistical analysis of variance (ANOVA) was performed followed by Fisher's Protected Least Significant Difference for pair wise comparison. All values are presented as mean +/- standard error of mean (SEM) and differences are considered statistically significant at $p<0.05$.

CONCLUSIONS & DISCUSSION

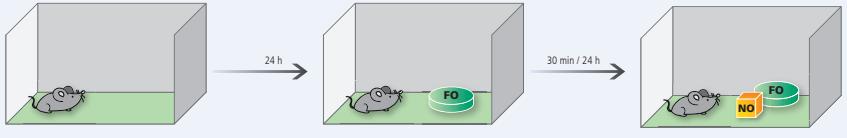
The multi-component/multi-target medication He-300

- Reverses Scopolamine-induced learning and memory deficits in mice.
- Improves memory and reduces natural forgetting.
- Improves learning and memory function with comparable efficacy to Donepezil.
- Has beneficial effects on hippocampal memory function in different species and in different memory and learning paradigms.

Due to its multi-component and well tolerated profile HE-300 is suggested as an alternative therapeutic option for the treatment of multi-factorial diseases such as Alzheimer's Disease.

NOVEL OBJECT RECOGNITION (NOR)

The novel object-recognition[2] (NOR) paradigm is based on spontaneous exploratory activity and on the tendency of rodents to spend more time exploring a novel object than a familiar object. The NOR is a common test for memory associated with the hippocampus function and has been shown to be sensitive to various pharmacological manipulations affecting memory processes[4].

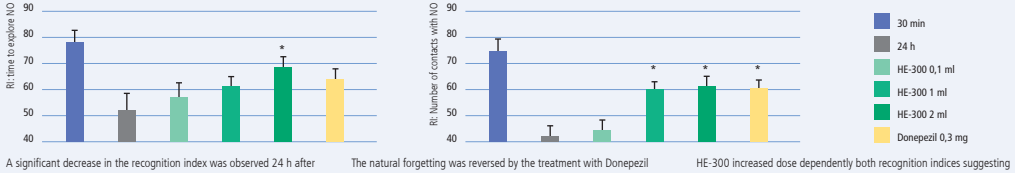


Habituation: Rats are allowed to explore the open-field for 15 min.

Acquisition trial: A familiar object (FO) is placed into the open field and rats are exposed for 10 min to the experimental situation.

Retention trial: A novel object (NO) is introduced to the open-field in addition to the familiar one. Rats are exposed to the situation for 10 min. The choice to explore the novel object reflects the use of learning and recognition memory.

RESULT: HE-300 IMPROVES NATURAL MEMORY PROCESSES IN THE NOVEL OBJECT RECOGNITION TEST



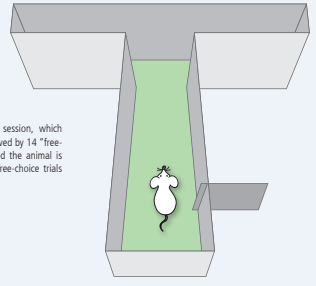
A significant decrease in the recognition index was observed 24 h after the acquisition trial (black column) indicating natural forgetting.

The natural forgetting was reversed by the treatment with Donepezil (0,3 mg). Donepezil increased contact (a) and time (b) recognition index significantly.

HE-300 increased dose dependently both recognition indices suggesting the improvement of natural memory processes. * $p < 0.05$ versus corresponding control group.

T-MAZE CONTINUOUS ALTERNATION TASK

T-maze is based on the natural behaviour to explore new environments. It is the innate tendency of healthy rodents to alternate freely both sides in a T-maze over a series of successive runs[1,3] (spontaneous alternations). This sequential procedure relies on working memory and is sensitive to various pharmacological manipulations affecting memory processes. [3,5]



The experiment consists of one single session, which starts with one "forced-choice" trial, followed by 14 "free-choice" trials. A session is terminated and the animal is removed from the maze as soon as 14 free-choice trials have been performed or after 10 minutes.

RESULT: HE-300 REVERSES SCOPOLAMINE INDUCED DEFICITS IN THE T-MAZE CONTINUOUS ALTERNATION TASK MODEL

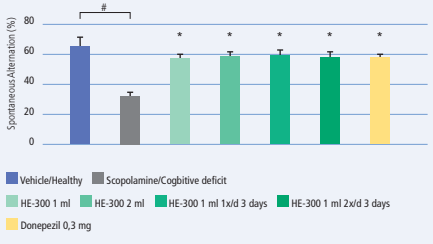


Figure 1 Scopolamine induced cognitive deficits reflected by decreased spontaneous alternation in comparison to untreated healthy controls. Donepezil (0.03 mg) improved the cognitive performance significantly about 72 % ($p<0.05$). HE-300 also significantly reversed scopolamine-induced cognitive deficits reflected by increased percentage of spontaneous alternation. * $p<0.05$ versus cognitive deficit group.

REFERENCES:

1. Barnes CA. Aging and the physiology of spatial memory. Neurobiol Aging. 1988 Sep-Dec;9(5-6):563-8
2. Ennaceur A, Delacour J. A new one-trial test for neurobiological studies of memory in rats. 1: Behavioral data. Behav Brain Res. 1988; 31:47-59.
3. Gerlai R. A new continuous alternation task in T-maze detects hippocampal dysfunction in mice. A strain comparison and lesion study. Behav Brain Res 1998 Sep;95(1):91-101.
4. Sambeth A, Riedel WJ, Smits LT, Blokland A.Cholinergic drugs affect novel object recognition in rats: relation with hippocampal EEG? Eur J Pharmacol. 2007; 572:151-9.
5. Spowart-Manning L, van der Staay FJ. The T-maze continuous alternation task for assessing the effects of putative cognition enhancers in the mouse. Behav Brain Res 2004 May 5;151(1-2):37-46.