Effect of Piracetam, Vinpocetine and Ginkgo Biloba Extract on Antipsychotic-Induced Impairment of Learning and Memory

Účinnost piracetamu, vinpocetinu a Ginkgo biloba na poruchy učení a paměti vyvolané antipsychotiky.

Abstract
Haloperidol is a classic neuroleptic drug with the known drawback that it induces motor abnormalities and impaired learning. Aim: To investigate the nootropic drugs piracetam, vinpocetine and extract of Ginkgo biloba for their ability to improve spatial memory in mice treated with haloperidol. Methods: Spatial memory was assessed by means of the Morris water maze (MWM) test. The effects of piracetam (50, 150 or 300 mg/kg, i.p.), vinpocetine (1, 2 or 4 mg/kg) and Ginkgo biloba extract (25, 50 or 150 mg/kg) were studied on working memory in mice treated with haloperidol (2 mg/kg, i.p.) to induce cognitive impairment [25]. The drugs were either co-administered with haloperidol or given 30 min before haloperidol administration. Results: The administration of haloperidol resulted in a significant increase in the time taken to locate a submerged test platform (latency). The time taken to locate the submerged platform was reduced dose-dependently by piracetam co-administered with haloperidol or given 30 min prior to the antipsychotic drug. Vinpocetine co-administered with haloperidol failed to improve cognitive performance, but vinpocetine at 4 mg/kg administered 30 min before haloperidol markedly reduced the time to locate the submerged platform. Mice treated with Ginkgo biloba extract showed worsening of their performance on the water maze test. Conclusion: Piracetam and vinpocetine, but not Ginkgo biloba extract, alleviate haloperidol-induced impairment of learning and memory in the MWM test. Human studies are needed to establish whether piracetam as well as vinpocetine may prove of value in improving cognition in patients treated with classic antipsychotic drugs.

Souhrn
Haloperidol je klasické neuroleptikum, které vyvolává motorické abnormality a poruchy učení. Cíl studie: Zhodnotit schopnost nootropik piracetamu, vinpocetinu a Ginkgo biloba zlepšit prostorovou paměť myší léčených haloperidolem. Měřena byla účinnost piracetamu (50, 150 nebo 300 mg/kg i.p.), vinpocetinu (1, 2 nebo 4 mg/kg) nebo Ginkgo biloba (25, 50 nebo 150 mg/kg) na pracovní paměť myší léčených haloperidolem (2 mg/kg, i.p.) podávaným k vyvolání kognitivní poruchy [25]. Léčivé látky byly buď podávány současně s haloperidolem, nebo 30 minut před podáním haloperidolu. Výsledky: Podání haloperidolu vedlo k významnému prodloužení latexce při hledání ponořené plošiny. Piracetam podaný současně s haloperidolem nebo 30 minut před antipsychotikem zkracoval v závislosti na dávce latexce při hledání ponořené plošiny. Vinpocetin podaný současně s haloperidolem zkrátil výkon nezlepšil, ale vinpocetin 4 mg/kg podaný 30 min před haloperidolem vyrazně zkrátil latexce při hledání ponořené plošiny. U myší léčených Ginkgo biloba došlo ke zhoršení výkonu ve vodním bludišti. Závěr: Piracetam a vinpocetin, avšak nikoli Ginkgo biloba, zlepšují porouchy učení a paměti vyvolané haloperidolem v Morrisově vodním bludišti. K potvrzení případné užitečnosti piracetamu a vinpocetinu při zlepšování kognice u pacientů léčených klasickými antipsychotiky je zapotřebí provést studie na lidských jedincích.

Key words
spatial memory – haloperidol – nootropics – mice

Omar M.E. Abdel-Salam1,2, Somaia A. Nada1
National Research Centre, Cairo, Egypt:
1 Department of Pharmacology
2 Toxicology and Narcotics

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Klíčová slova
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**Introduction**

Memory, or the retention of learned information, is fundamental to human beings. Memory impairment such as that occurring in normal aging or in pathological conditions, e.g., Alzheimer’s disease, is a serious medical and social problem. At present, few drugs are available for the treatment of memory disorders. These include the pyrrolidine derivative piracetam [1], the synthetic vircamine derivative vinpocetine [2] and standardized extracts of Ginkgo biloba leaves [3]. Although these drugs belong to distinct and different chemical classes, they share the term “nootropic”, introduced by Giurgea in 1973 [4], to indicate a category of drugs that enhance memory, facilitates learning and protects memory processes against conditions that tend to disrupt them.

Piracetam, a pyrrolidine derivative (2-oxo-1-pyrrolidine acetamide), was the first nootropic (from the Greek noos ‘mind’ and tropos, ‘growth, movement towards’) drug to be introduced into clinical practice. The drug has been shown to facilitate learning and to prevent the development of amnesia under various experimental conditions [1]. Piracetam enhanced recovery from aphasia after stroke [5] and improved cognitive function in the elderly [6] and after coronary artery bypass [7]. The drug reversed hippocampal membrane alterations in Alzheimer’s disease [8] and inhibited the lipid-destabilizing effect of the amyloid peptide Abeta C-terminal fragment [9].

Vinpocetine (vinpocetine-ethyl apovincamine), is a synthetic derivative of the alkaloid vincamine, an extract of the lesser periwinkle (Vinca minor), a wildflower. Vinpocetine is widely used to improve cognitive function in patients with cerebrovascular disease in consideration of its ability to increase cerebral blood flow, which in turn increases regional cerebral glucose uptake [2,10]. In patients with ischemic stroke and mild cognitive impairment, vinpocetine favorably influenced the cognitive status in patients with chronic hypoperfusion [11]. The drug prevented scopolamine- and hypoxia-induced impairment of passive avoidance retention in rats [12] and improved short-term memory processes in patients with flunitrazepam-induced impairment of memory [13].

Standardized extracts of the leaves of Ginkgo biloba (EGb 761) are widely used as cognitive and memory enhancers in the cerebral insufficiency that occurs during normal aging or that arises out of vascular or degenerative dementias, but with variable outcome [14,15]. Extracts of Ginkgo biloba contain 24% ginkgo-flavone glycosides and 6% terpenoids (ginkgolides, bilobalide). The herb has been shown to possess antioxidant and free radical scavenging activities [16], anti-inflammatory [17], vasodilatory [18] and rheological [19] properties. Extracts of Ginkgo biloba may possess amyloid precursor protein lowering capacity as well [20].

Cognitive impairment in schizophrenia is frequent. Spatial working memory or short-term place memory is impaired in schizophrenia and the effect of antipsychotics on cognition in patients with schizophrenia is an important issue that generates considerable debate. Studies have suggested worsening of memory tasks associated with the use of the typical antipsychotic haloperidol in healthy volunteers [21–23] and in schizophrenic patients [24] compared with patients treated with atypical neuroleptics such as risperidone, olanzapine, and ziprasidone, which improved cognition in several studies [25]. Researchers found remarkably reduced psychomotor performance in the haloperidol-treated group of schizophrenic patients compared with patients treated with atypical neuroleptics [24]. Procedural learning was also found to be poorer in haloperidol-treated patients than in normal control subjects, while no difference could be observed between olanzapine-treated patients and normal control subjects [23]. The view that atypical antipsychotics improve memory in patients with schizophrenia is, however, not supported by all studies. Short-term administration of olanzapine, and not of haloperidol, impeded several aspects of psychomotor function and verbal memory in healthy volunteers [26]. Not all domains of cognition seem to be equally affected by different antipsychotics and risperidone, olanzapine, and haloperidol did not improve social cognition in schizophrenia [27]. Cognitive improvement associated with the administration of antipsychotic medication may be a manifestation of improvement in general cortical information processing [28]. Other studies, however, have suggested that improvements in cognition in schizophrenia treated with second-generation antipsychotic medications might reflect simple practice effects (i.e., exposure, familiarity, and/or procedural learning), while medication effects on cognition remain modest [29]. In any event, there is clearly a need to treat patients with schizophrenia with cognition-enhancing medications.

In experimental animals, haloperidol, which blocks D2 dopamine receptors in the striatum, causes impairment of memory retention in terms of latency time to find the original location of the platform in a water-maze task [30]. Haloperidol as well as clozapine impaired the acquisition process and consolidation processes respectively in step-through test. Both drugs impaired spatial learning function in mice in the water maze task [31]. The present study was therefore designed to investigate the effect of the memory enhancing drugs piracetam, vinpocetine and Ginkgo biloba extract in terms of their ability to improve spatial memory in mice treated with haloperidol.

**Materials and methods**

**Animals**

Swiss male albinos mice of 20–22 g body weight were employed. Standard laboratory food and water were provided ad libitum. Animal procedures were performed in accordance with the Ethics Committee of the National Research Centre and followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85–23, revised 1985). Equal groups of six mice each were used in all experiments.

**Cognitive testing**

The Morris water maze (MWM) was employed to test spatial learning and memory. The MWM is a paradigm that requires the mice to use spatial memory to find a hidden platform just below the surface of a pool of water, and to remember its location from a previous trial [32]. The mice must therefore use distal cues to effectively locate the platform. Accurate navigation is rewarded by escape from the pool. The maze consisted of a glass tank narrowed to 20 cm wide, 40 cm in height, 70 cm in length, filled to a depth of 21 cm with water maintained...
At 25 °C. The glass escape platform was hidden from sight, submerged 1 cm below the surface of the water at the end of the tank [33]. The effect of piracetam (50, 150 or 300 mg/kg, i.p.), vinpocetine (1, 2 or 4 mg/kg) or Ginkgo biloba extract (25, 50 or 150 mg/kg) on working memory was studied in mice treated with haloperidol (2 mg/kg, i.p.) to induce cognitive impairment [30]. Drugs were either co-administered with haloperidol or given 30 min before haloperidol administration in order to see whether a difference exists or not when cognitive enhancers are given prior to the drug-produced memory impairment. Mice rapidly learn to swim directly to the escape platform and climb out. Once a mouse reached the platform, it remained there for 15 sec (trial 1; reference memory or acquisition trial). At the end of each trial, the mouse was towel-dried, returned to its home cage (where a heat lamp was available), and 3 min elapsed before the next trial (trials 2 and 3; working memory or retrieval trial), using the same platform location and start position as trial 1. The latency to find the platform (in seconds) was assessed with a stopwatch.

**Drugs**

Haloperidol (Kahira Pharm and Chem. Co., Cairo, ARE), vinpocetine (Vinporal, Amrya Pharm. Ind., Cairo, ARE), piracetam (Nootropi, Chemical Industries Development; CID, Cairo, ARE), Ginkgo biloba extract (EMA Pharm. Co., Cairo, ARE). All drugs were dissolved in isotonic (0.9% NaCl) saline solution immediately before use. The doses of drugs used in the study were based upon the human dose after conversion to that for mice, after conversion tables by Paget and Barnes [34]. The dose of haloperidol used in the study (2 mg/kg) was chosen on the basis of similar studies by Terry et al [35,36]. The dose would be expected to achieve comparable (and therapeutically relevant) D2 receptor occupancy values in vivo (i.e., in the range 65–80%) and based on the fact that haloperidol is metabolized over three times faster in rats than in humans.

**Statistical Analysis**

Data are expressed as mean ± SEM. The data were analyzed by one way ANOVA and by repeated measures (session × treatment) ANOVA, followed by Duncan’s multiple range test, using SPSS software (SAS Institute Inc., Cary, NC). A probability value of less than 0.05 was considered statistically significant.

**Results**

**Effect of nootropics on haloperidol-induced memory impairment**

Spatial memory was tested in the Morris water maze test. Haloperidol substantially impaired water maze performance. The time taken to find the escape platform (latency) was significantly delayed by haloperidol (2 mg/kg, i.p.). Animals given piracetam co-administered with haloperidol or given 30 min prior to the antipsychotic drug showed significantly shorter latencies, which indicated that learning had occurred immediately (Fig. 1). All groups exhibited learning and improved their performance with training, analyzed as the time taken to reach the hidden platform (F = 11.58; p < 0.0001). There was also a significant effect of treatment (F = 136.96; p < 0.0001) and a significant treatment × session interaction (F = 2.87; p = 0.002).

Post-hoc comparison indicated significantly shorter latencies for location of the hidden platform on the part of all treated groups in trials 1, 3 and 3 compared with the haloperidol control group. Furthermore, in trial 2, the group treated with the highest dose of piracetam showed significantly shorter latencies than all other treatment groups.

Vinpocetine co-administered with haloperidol failed to improve cognitive performance on water maze test, but vinpocetine at 4 mg/kg administered 30 min before haloperidol markedly reduced the latencies for location of the submerged platform (Fig. 2). There was a significant drug effect (F = 105.34; p < 0.0001), but insignificant session effect (F = 1.99; p = 0.143) or treatment × session interaction (F = 0.434; p = 0.96).

In trial 1, post-hoc comparisons indicated significantly shorter escape latencies for mice co-treated or pretreated with haloperidol and any dose of vinpocetine (0.9% NaCl) saline solution immediately after haloperidol administration. At time of haloperidol, the latency for location of the submerged platform was significantly different between haloperidol control and all treated groups (P < 0.0001) and between haloperidol and any dose of vinpocetine (P < 0.0001). At 30 min before haloperidol, the latency for location of the submerged platform was significantly different between haloperidol and any dose of vinpocetine (P < 0.0001) and between haloperidol and any dose of vinpocetine (P < 0.0001).

![Fig. 1. Effect of piracetam on haloperidol-induced (2 mg/kg, i.p.) impairment of learning and memory of mice in the Morris water maze test.](image-url)

Piracetam was given intraperitoneally (i.p.) either at the time of haloperidol administration or 30 min before haloperidol administration. The latency (in seconds) to find the platform was determined for control and drug-treated groups. Each mouse was given three trials (columns 1, 2, 3) (trial 1: reference memory or acquisition trial (first column), trials 2 and 3: working memory or retrieval trial (second and third column) which used the same platform location and start. Data represent mean values (± SE) of 6 mice per group. Statistically significant differences vs. haloperidol control group are indicated by asterisks. For other group differences, see text.
Effect of piracetam, vinpocetine and Ginkgo Biloba extract


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with 4 mg/kg vinpocetine compared with other treatment groups. In trial 2, co-treatment with 2–4 mg/kg vinpocetine as well as pretreatment with 1–4 mg/kg vinpocetine was associated with significantly shorter escape latencies compared with haloperidol control. Meanwhile, co-treatment or pretreatment with 4 mg/kg vinpocetine resulted in significantly shorter escape latencies compared with other treatment groups. Thus the highest dose of vinpocetine resulted in significantly shorter escape latencies in all trials compared with the haloperidol-control group.

Mice treated with Ginkgo biloba extract showed worsening of their performance on the water maze test with markedly increased time to find the hidden platform (Fig. 3). Repeated ANOVA mea-

Fig. 3. Effect of Ginkgo biloba extract on haloperidol-induced (2 mg/kg, i.p.) impairment of learning and memory of mice in the Morris water maze test.

Ginkgo biloba extract was given intraperitoneally (i.p.) either at the time of haloperidol administration or 30 min before haloperidol administration. The latency (in seconds) to find the platform was determined for control and drug-treated groups. Each mouse was given three trials (columns 1, 2, 3) (trial 1: reference memory or acquisition trial (first column), trials 2 and 3: working memory or retrieval trial (second and third column)) which used the same platform location and start. Data represent mean values (±SE) of 6 mice per group. Statistically significant differences vs. haloperidol control group are indicated by asterisks. For other group differences please refer to the text.
sures indicated a significant treatment effect, $F = 92.5; p < 0.0001$, but insignificant trial effect, $F = 1.98; p = 0.144$ or treatment by trial interaction, $F = 1.74; p = 0.64$.

Post-hoc comparisons revealed a significant increase in escape latencies in trial 1, 2 and 3 on co-treatment with 150 mg/kg ginkgo and by pretreatment with 50 or 150 mg/kg of Ginkgo biloba extract compared with other treatment groups. In addition, pretreatment with 150 mg/kg of Ginkgo biloba extract was associated with significant increase in escape latencies in trial 2 and 3 compared with other treatment groups.

**Discussion**

In the current study, haloperidol substantially impaired the water maze performance of mice. Both the acquisition and retention of information were impaired by the drug. The dopaminergic system plays an important role in memory processes [37,38]. Studies have suggested that D2-like receptors have a greater contribution to make than D1-like receptors to both spatial working memory and object-location associative memory [39].

The D2-dopaminergic system is involved in the induction of basolateral amygdala to long-term potentiation of the dentate gyrus [40]. Haloperidol impaired spatial working memory performance and planning ability in healthy volunteers [21,22] and worsened recent autobiographical memory scores of patients with Alzheimer’s disease [41]. In experimental animals haloperidol, and to lesser extent olanzepine and risperidone, impaired working memory performance [42].

In the current study, the dose of haloperidol used was shown to impair locomotor activity in a previous task [43] and drug influence on motor activity cannot be ruled out, but the water maze test is primarily a test of cognition (spatial learning/memory) [44]. Other workers have reached the conclusion that the negative effects of haloperidol in the water maze task are likely to be memory-related [35].

The current study investigated the effect of the nootropic drugs piracetam, vinpocetine and Ginkgo biloba extract on haloperidol-induced impairment of learning and memory in the water maze test. Favorable effects were observed after piracetam and the highest dose of vinpocetine examined, but not after Ginkgo biloba extract. Piracetam administered either as co-treatment or pretreatment markedly alleviated the impairment of learning and memory induced by haloperidol. The drug appeared to be nearly equally effective at all doses examined (50, 100 and 300 mg/kg). Piracetam has proved effective in several models of amnesia. It has been shown to facilitate learning and retrieval of information and protect the brain from physical and chemical intoxication [45]. It reverses the amnesia induced by scopolamine, electroconvulsive shock and morphine as well as that caused by hypoxia [46,47].

Piracetam has negated the amnesiastic effect of 6-hydroxydopamine and restored to control values the noradrenaline level in the frontal cortex and hippocampus [48]. It has been shown to increase cortical and striatal monoamines [49,50], which might underlie its cognitive enhancing properties.

The latency of haloperidol-treated mice in location of the submerged platform in the MWM test was also reduced by 4 mg/kg vinpocetine given either at the same time as haloperidol administration or 30 min prior to haloperidol. Other researchers have shown that vinpocetine prevented scopolamine- and hypoxia-induced impairment of passive avoidance retention in rats [12]. Vinpocetine and its main metabolite cis-apovincaminic acid protects against NMDA-induced neurotoxicity in a rat model of dementia. Behavioural deficits, such as impaired recognition of novel objects and spatial learning performance in the Morris maze, lesion size and microglia activation, have been markedly alleviated by vinpocetine and cis-apovincaminic acid [51].

The drug improved fluunitrazepam-induced impairment of memory in healthy volunteers treated with fluunitrazepam [13], and led to significant cognitive improvement in elderly patients with chronic cerebral dysfunction [52] as well as in patients with ischemic stroke and mild cognitive impairment [11]. Other researchers found no clear benefit demonstrated in patients with acute ischemic stroke [53]. The drug reduced accumulation of reactive oxygen species and blocked the inhibition of the mitochondrial respiratory chain complexes II–III and IV induced in cells by toxic concentrations of Aβ peptides [54]. In vitro, vinpocetine in a 1–50 µM/ml concentration range protected against glutamate excitotoxicity in primary cortical neuronal cultures [55]. The drug binds to the peripheral-type benzodiazepine receptor involved in the mitochondrial transition pore complex [56] and reduces the decrease in mitochondrial inner membrane potential induced by glutamate exposure [55]. These properties are likely to mediate the beneficial influence of vinpocetine in cerebrovascular disease. In patients with Alzheimer’s disease, vinpocetine up to 60 mg per day, however, failed to improve cognition or overall functioning [57].

**Ginkgo biloba** extract extracts are widely used to treat memory disorders, although their value is not yet clear. In one study in patients with mild cognitive impairment, about half of the patients treated with Ginkgo biloba extract experienced an improvement in memory and their ability to concentrate, as well as a decrease in symptoms of forgetfulness [58]. In a randomized clinical trial, Ginkgo biloba extract neither altered the risk of progression from normal to clinical dementia nor protected against decline in memory function [59]. In another study, Ginkgo biloba extract at 120 mg twice a day was not effective in reducing either the overall incidence rate of dementia or Alzheimer’s disease incidence in elderly individuals with normal cognition or those with mild cognitive impairment [60]. Ginkgo biloba extract (120 mg per day) had no significant effect on a wide range of cognitive abilities, executive function, attention and mood in healthy older adults and in young adults [61]. In healthy young volunteers, Ginkgo biloba extract administration improved quality of memory 1 and 4 h post-dosing, but decreased the speed of attention task performance [62]. In rats subjected to chronic restraint stress, Ginkgo biloba extract decreased hippocampal neuronal loss and cognitive dysfunction [63] and improved spatial memory [64]. It was also effective in reducing, at least partially, both cognitive impairments and hippocampal damage after transient forebrain ischemia in rats [65]. Others have suggested that Ginkgo biloba extract does not enhance short-term working memory or long-term memory reference, but rather promotes learning of spatial information [66] and that Ginkgo biloba extract does not offer any continued beneficial effects in an already-learned working me-
mory task [67]. The effects of Ginkgo bi-
loba extract on spatial memory have been as-
cribed to cholinergic activity and per-
haps partly to a histaminergic mechanism [68], to increased synaptic plasticity [69] and to increased level of 5-hydroxytrypta-
mine in the hippocampus [70]. In this
study, the administration of Ginkgo bi-
loba extract even made impairment of
cognitive performance induced by hal-
operidol worse in the water maze test, lea-
ting to higher latencies of location for the
platform.

In summary, the current study showed
that piracetam and vinpocetine, but not the
herbal remedy Ginkgo biloba extract, alleviated the impairment of learning and memory induced by the typical anti-
psychotic haloperidol. Further studies are
warranted in patients with schizophrenia to ascertain whether Ginkgo biloba extract
might be suitable for improving co-
gnitive function in patients treated
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The current study showed that piracetam and vinpocetine, but not the herbal remedy Ginkgo biloba extract, alleviated the impairment of learning and memory induced by the typical anti-psychotic haloperidol. Further studies are warranted in patients with schizophrenia to ascertain whether Ginkgo biloba extract might be suitable for improving cognitive function in patients treated with classic antipsychotic drugs.

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