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Piracetam reverses haloperidol-induced catalepsy in mice

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Aim: To investigate the memory-enhancing drugs piracetam, vinpocetine, and ginkgo biloba for their ability to reduce catalepsy in mice treated with haloperidol. Haloperidol is a classic neuroleptic drug that induces motor abnormalities and cognitive impairment due to a blockade of dopamine D2 receptors in the striatum.

Materials and methods: Catalepsy was induced by intraperitoneal haloperidol (2 mg/kg) administration. The drugs being tested were either administered intraperitoneally (IP) along with the dosage of haloperidol or 30 min prior to the introduction of the haloperidol. Catalepsy was measured using the bar test.

Results: The administration of haloperidol (2 mg/kg, IP) resulted in significant catalepsy. Piracetam (in dosages of 50, 100, and 300 mg/kg) given IP at the time of haloperidol administration reduced the duration of catalepsy by 24.4%, 32.3%, and 48.2%, respectively. Piracetam given as a 30-min pretreatment reduced the duration of catalepsy by 59.5%, 72.3%, and 78.2%, respectively. Vinpocetine coadministered IP with haloperidol did not modify catalepsy, but given as a 30-min pretreatment, the drug increased catalepsy duration by 53.5%, 53.6%, and 65.1%, respectively. Ginkgo biloba coadministered IP with haloperidol at 25, 50, or 150 mg/kg increased catalepsy duration by 13.6%-17.1%. Ginkgo biloba given 30 min prior to haloperidol increased catalepsy duration by 29.1%, 35.1%, and 37.2%, respectively.

Conclusion: The present study indicates that the nootropic drug piracetam reduces haloperidol-induced catalepsy in mice.

Key words: Catalepsy, haloperidol, piracetam, vinpocetine, ginkgo biloba, mice

Introduction

Typical antipsychotics used in schizophrenia treatment, such as haloperidol, produce extrapyramidal side effects, which are attributed to a blockade of D2 in the striatum (1). Catalepsy is a state of postural immobility (akinesia) with muscular rigidity. Catalepsy induced by haloperidol is considered a rodent model of the Parkinson’s-like side effects caused by typical antipsychotics in humans (2). Antipsychotics can also induce deficits in working memory (3,4) and, accordingly, drugs that improve learning and memory are often prescribed to counteract the cognitive impairment.

Piracetam is a pyrrolidone derivative (2-oxo-1-pyrrolidin acetamide) that has been shown to facilitate learning and prevent the development of amnesia under different experimental conditions (5). In clinical practice, the drug has been shown to enhance recovery from aphasia after stroke (6), and to improve cognitive function in the elderly (7) and after coronary artery bypass (8). It also improved degenerative cerebellar ataxia (9) and prevented alcohol withdrawal delirium (10).

Vinpocetine (vinpocetine-ethyl apovincaminate) is a synthetic derivative of the alkaloid vincamine, an extract of periwinkle (Vinca minor), and is widely used to improve the cognitive...
function of patients with cerebrovascular disease. This effect is a result of its ability to increase cerebral blood flow, which in turn increases the regional cerebral glucose uptake (11). It also significantly decreased the risk of transient ischemic attacks and strokes in patients with chronic cerebrovascular insufficiency (12). The drug displayed memory-protective and memory-enhancing properties (13,14). Vinpocetine is a phosphodiesterase 1 inhibitor (15) and a blocker of voltage-gated Na+ channels (16), which are thought to be especially relevant to its anticonvulsant and neuroprotective effects. Vinpocetine also inhibited lipid peroxidation stimulated by ascorbate/Fe2+ in rat brain synaptosomes (17).

Standardized extracts from the leaves of ginkgo biloba are widely used to improve cognition and memory in cases of cerebral insufficiency (18,19). Extracts of ginkgo biloba contain 24% ginkgo-flavone glycosides and 6% terpenoids (ginkgolides, bilobalide). The beneficial effects of ginkgo biloba have been ascribed to its antioxidant and free radical scavenging activities (20), as well as its antiinflammatory (21), vasodilatory (22), and rheological (23) properties. Moreover, ginkgolides, especially ginkgolides B and C, are potent platelet-activating factor antagonists (24).

Apart from being used to improve cognitive functions in the elderly and in different disease processes, the aforementioned nootropic drugs might also affect motor circuits in the brain and could therefore be used in the treatment of movement disorders or with conditions that have adverse motor influences. For example, piracetam has been used in the cortical myoclonus, where it resulted in a significant improvement in motor performance (25). It improved gait in patients with cerebellar ataxia (9) and appeared to be effective in reducing the symptoms of tardive dyskinesia in schizophrenic patients on antipsychotic treatment (26). Vinpocetine is a blocker of voltage-gated sodium channels. Such channels are responsible for action potential generation and propagation, and an increased activity of these channels accompanies disease states such as epilepsy, chronic pain, neurodegenerative diseases, and spasticity (27). Vinpocetine has been reported to decrease spontaneous locomotor activity in rats (28). Ginkgo biloba delayed the deterioration of motor functions in rats with chronic cerebral insufficiency (29). Furthermore, these drugs also displayed a capacity for altering neurotransmitter levels in the brain and dopamine activity in the striatum (30-33), which is relevant to the cataleptic state.

The aim of this study was therefore to investigate the effect of the memory-enhancing drugs piracetam, vinpocetine, and ginkgo biloba on motor symptoms in an animal model of haloperidol-induced Parkinson’s disease.

Materials and methods

Animals

Swiss male albino mice with a body weight of 20-22 g were used in this study. 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 Institute of Health’s Guide for Care and Use of Laboratory Animals (34). Equal groups were used in all experiments, with 6 mice in each group. All drug dosages used in the study were based upon the human dose converted to meet the physical parameters of the rats, as detailed in the Paget and Barnes conversion tables (35).

Haloperidol-induced catalepsy

Catalepsy, defined as a reduced ability to initiate movement and a failure to achieve correct posture, was measured by the bar test. Mice were positioned so that their hindquarters were on the bench and their forelimbs rested on a 1-cm diameter horizontal bar that was 4 cm above the bench. Mice were judged to be cataleptic if they maintained this position for 30 s or more. The length of time for which the mouse maintained this position was recorded with a stopwatch with a maximum duration of 180 s. This procedure was performed 30 min after the administration of haloperidol (2 mg/kg, IP). The test drugs, i.e. piracetam (100, 150, or 300 mg/kg, IP), vinpocetine (1, 2, or 4 mg/kg), and ginkgo biloba (25, 50, or 150 mg/kg), were given either at the time of the haloperidol administration or 30 min prior to the haloperidol administration. Control animals received 0.9% saline (the vehicle).
**Statistical analyses**

Data were expressed as mean ± SE. Differences between treatment groups were determined using one-way ANOVA tests followed by multiple comparison by Duncan’s multiple range test. A probability value less than 0.05 was considered statistically significant.

**Results**

At a dosage of 2 mg/kg, the IP administration of haloperidol produced a significant cataleptic response. The duration of haloperidol-induced catalepsy was significantly reduced by the simultaneous administration of 50, 100, and 300 mg/kg dosages of piracetam, with the reduction figures being 24.4%, 32.3%, and 48.2% (P < 0.05), respectively. Piracetam given 30 min prior to haloperidol further reduced the duration of catalepsy by 59.5%, 72.3%, and 78.2% (P < 0.05), respectively (Figure 1). Findings showed that the duration of catalepsy was significantly shorter when piracetam was given 30 min prior to the administration of haloperidol than when the same dosages were given to the mice at the time of haloperidol administration (P < 0.05). Vinpocetine (in doses of 1, 2, or 4 mg/kg) had no significant effect on haloperidol catalepsy when given at the same time as the injection of haloperidol. In contrast, the same dosages of vinpocetine administered 30 min before the haloperidol injection significantly increased the duration of catalepsy, by 53.5%, 53.6%, and 65.1% (P < 0.05), respectively (Figure 2). The duration of catalepsy was significantly higher when vinpocetine was given 30 min before haloperidol as compared with the results seen in mice given vinpocetine at the same time as the haloperidol administration (P < 0.05). The administration of 25, 50, or 150 mg/kg of ginkgo biloba at the time of the haloperidol injection increased catalepsy duration by only 13.6%-17.1% (P > 0.05). In contrast, ginkgo biloba given 30 min prior to haloperidol resulted in a significant increase in the duration of the catalepsy response, with data indicating an increase of 29.1%, 35.1%, and 37.2% (P < 0.05), respectively (Figure 3). The duration of

![Figure 1](image1.png)  
**Figure 1.** Effect of piracetam on haloperidol-induced (2 mg/kg, IP) catalepsy in mice. Piracetam was given IP either at the time of the haloperidol administration or 30 min prior to that injection. Data represent mean values ± SE of 6 mice per group and the percentage change (%) in comparison with the control animals. Statistical differences between the test groups and the control group are indicated by asterisks (*). The plus sign (+) indicates a significant change from the corresponding treatment group given piracetam at the time of the haloperidol administration.

![Figure 2](image2.png)  
**Figure 2.** Effect of vinpocetine on haloperidol-induced (2 mg/kg, IP) catalepsy in mice. Vinpocetine was given IP either at the time of the haloperidol administration or 30 min prior to that injection. Data represent mean values ± SE of 6 mice per group and the percentage change (%) in comparison with the control animals. Statistical differences between the test groups and the control group are indicated by asterisks (*). The plus sign (+) indicates a significant change from the corresponding treatment group given vinpocetine at the time of the haloperidol administration.
Piracetam and catalepsy

catalepsy was significantly higher when ginkgo biloba was given 30 min before haloperidol, as compared with mice given ginkgo biloba at the same time as the administration of haloperidol (P < 0.05).

Discussion

The present study provided evidence that catalepsy induced by the antipsychotic drug haloperidol is reduced by the administration of the nootropic drug piracetam and increased by vinpocetine and ginkgo biloba. Typical antipsychotics such as haloperidol, a dopamine D2 receptor antagonist, produce extrapyramidal side effects, which are attributed to a blockade of D2 in the striatum (1). Rats treated with haloperidol show akinesia and rigidity (i.e. catalepsy), effects that are mediated by a blockade of striatal D2 receptors (2). Akinetic catalepsy induced in rats by haloperidol can model human Parkinson’s disease. Haloperidol remains effective in inducing catalepsy and striatal Fos/Jun expression in the D1 mutants, and these behavioral and neural effects can be blocked by D2 dopamine receptor agonists (36). Catalepsy occurs when more than 80% of D2 receptors are occupied by the drug (37). Catalepsy is also driven by the excitatory adenosine and glutamatergic inputs acting on adenosine A2A and N-methyl-D-aspartate (NMDA) receptors in the striatum. This is because NMDA receptor antagonists (38), the nonselective adenosine receptor antagonist caffeine, selective A1, and selective A2A antagonists decreased haloperidol-induced catalepsy in rats (38,39). Catalepsy is also reduced by alpha2 receptor antagonists (alpha2C or alpha2A) (40) or 5-HT1A agonists (41), as well as by metabotropic glutamate receptor 4 agonists (42). Despite having a striatal D2 receptor occupancy similar to classical agents, atypical antipsychotics are less likely to cause extrapyramidal side effects because of their ability to activate 5-HT1A receptors (43).

Piracetam is a drug used to enhance memory and cognitive performance in the elderly or after cerebrovascular accidents (6) by increasing blood flow and affecting membrane fluidity (44) and glucose transport into the cells (45). Piracetam, however, is not without effects on intracortical neurotransmitters. Piracetam restored the number of active GABA-A receptors in rats made anxiolytic and depressed by prolonged hypokinesia (46). It also inhibited the effect of flumazenil and therefore may be shown to act on the benzodiazepine site of the GABA-benzodiazepine receptor complex (47). Drug-inhibited monoamine uptake (dopamine, noradrenaline, serotonin) in cortical and striatal synaptosomes (30) increased K+-induced dopamine release from rat striatum in aged rats (31). Thus, piracetam is capable of modifying the dopaminergic activity of the rat striatum, thereby stimulating the neuromediator release (31). Studies also suggested the involvement of the dopaminergic system in the excitatory effects of piracetam (100 mg/kg) on foot shock-induced aggressive behavior in mice, which was blocked by treatment with haloperidol (48). The effect of piracetam on dopaminergic transmission might be of particular relevance to the inhibition of haloperidol-induced catalepsy observed in the present study. Because catalepsy is thought to be a good predictor of extrapyramidal symptoms in humans, treatment with piracetam might decrease the occurrence or severity of extrapyramidal symptoms induced in humans by the use of antipsychotics. Other
Researchers have reported that piracetam caused an increase of haloperidol-induced catalepsy in rats, but those findings reflect studies that tested a dose considerably higher than those used in the present study (1000 mg/kg) (49); studies that examined a piracetam dosage of 500 mg/kg showed markedly inhibited haloperidol catalepsy (50).

In the present study, vinpocetine increased catalepsy when administered prior to haloperidol. Other studies have indicated that vinpocetine (5-100 mg/kg PO) did not antagonize reserpine-induced catalepsy, and it did not impair rotarod performance or produce ataxia in mice (28). There is limited information on the effect of vinpocetine on dopaminergic neurotransmission. In striatal slices, vinpocetine reduced the efflux of dopamine and acetylcholine evoked by glutamate, quisqualate, and NMDA (51), and it inhibited the release of dopamine evoked by veratridine reversal of the dopamine transporter (32). These effects could explain the present study’s observed increase in catalepsy duration after the introduction of vinpocetine. Other studies found no inhibitory activity for vinpocetine and its major metabolite, apovincaminic acid, in monoamine receptor binding assays or in synaptosomal uptake assays performed in vitro (52). Vinpocetine inhibits the permeability of voltage-sensitive presynaptic Na+ channels, which selectively inhibits the transporter-mediated release of all neurotransmitters (32).

Some studies have suggested that, in light of its antioxidant properties, ginkgo biloba might prove valuable in the treatment of PD. One of its diterpenes, ginkgolide B, inhibited apoptosis induced by 6-hydroxydopamine by decreasing the intracellular calcium concentration (53). In a mouse model of Parkinson’s disease caused by the administration of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a compound that causes nigrostriatal dopaminergic degeneration, ginkgo biloba attenuated the toxin-induced loss of striatal dopamine levels and tyrosine hydroxylase immunostaining in the striatum and substantia nigra pars compacta. This neuroprotective effect of ginkgo biloba was associated with the inhibition of lipid peroxidation and the reduction of superoxide radical production (54). Extracts of ginkgo biloba leaves have been found to influence dopaminergic neurotransmission in the brain. Ginkgo biloba increased the extracellular concentration of dopamine in the prefrontal cortex of rats and upregulated the subgroup of dopamine receptors in the frontal cortex (55). The extract also increased the level of serotonin (5-HT) in the hippocampus and 5-HIAA (5-HT metabolite) in the prefrontal cortex (56). In other studies, norepinephrine, serotonin, and dopamine uptake transporters and MAO activity were inhibited by ginkgo biloba in vitro (33). Ginkgo biloba inhibited NMDA-evoked currents and Na+ channels in cultured cortical cells (57). In the present study, however, haloperidol-induced catalepsy was increased by the administration of ginkgo biloba (25, 50, and 150 mg/kg). Other researchers have also found that doses of 40 and 80 mg/kg of ginkgo biloba extract significantly enhanced haloperidol- and L-nitroarginine-induced catalepsy in mice (58). The mechanism(s) behind this effect of ginkgo is or are not clear and this issue awaits further studies.

In conclusion, the present paper provides evidence that piracetam is able to improve haloperidol-induced catalepsy in mice. In contrast, the administration of vinpocetine or ginkgo biloba was associated with a worsening of catalepsy.

References

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