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Vinpocetine: Nootropic Effects on Scopolamine-Induced and Hypoxia-Induced Retrieval Deficits of a Step-Through Passive Avoidance Response in Rats

VICTOR J. DENOBLE,[1] SUSAN J. REPETTI, LAURA W. GELPKE, LISA M. WOOD AND KEVIN L. KEIM

Ayerst Laboratories Research, Inc., CN 8000, Princeton, NJ 08540

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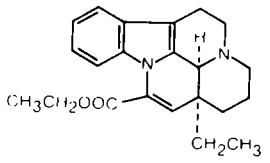
DENOBLE, V J , S J REPETTI, L W GELPKE, L M WOOD AND K L KEIM *Vinpocetine Nootropic effects on scopolamine-induced and hypoxia-induced retrieval deficits of a step-through passive avoidance response in rats* PHARMACOL BIOCHEM BEHAV 24(4) 1123–1128, 1986 —Vinpocetine, vincamine, aniracetam, and Hydergine®, compounds with purported cognition activating activity, were evaluated for their ability to prevent scopolamine-induced and hypoxia-induced impairment of passive avoidance retention (24 hr) in rats Vinpocetine (peak effect dose [PED]=200 mg/kg PO), aniracetam (PED=100 mg/kg PO), vincamine (PED=30 mg/kg PO), and Hydergine® (PED=1 mg/kg PO) prevented memory disruption by scopolamine Vinpocetine (PED=3 mg/kg PO) and aniracetam (PED=30 mg/kg PO) were also effective in preventing disruption of passive avoidance retention impaired by 7% oxygen hypoxia In contrast, Hydergine® (0 05 to 3 mg/kg PO) and vincamine (0 3 to 100 mg/kg PO) were not effective against hypoxia-induced impairment. Hydergine® at doses >10 mg/kg PO markedly impaired motor function In both tests the protection was dose-related for all test substances in an inverted U-shaped manner Mecamylamine (1, 3, 10 mg/kg SC), (−)-nicotine (0 1 to 0 4 mg/kg SC), apovincaminic acid (1–400 mg/kg PO) and pemoline (1–100 mg/kg PO) did not protect against memory impairment induced by either procedure These data support the view that vinpocetine, a compound chemically distinct from the pyrrolidinones, has a cognitive activating ability as defined in models of both scopolamine-induced and hypoxia-induced memory impairment in rats

Vinpocetine Vincamine Hydergine® Aniracetam Passive avoidance Scopolamine Hypoxia Rats

A common symptom of aging is a gradual deterioration of memory function [16,27] This has led to a search for therapeutic agents that improve cognitive function. Several studies have provided evidence that disruption of central cholinergic pathways results in impaired memory processes For example, administration of cholinergic receptor antagonists such as scopolamine and atropine or treatment with inhibitors of choline acetyltransferase, results in memory impairments in both humans [16] and animals [13, 15, 24] Retention deficits induced by scopolamine administration have been reversed by physostigmine [1,2] and by certain nootropic agents [11, 13, 43]. In addition, conditions that reduce the energy supply to the brain, such as hypoxia or cerebral ischemia, also cause amnesia or learning deficits [28,34], this learning/memory impairment can also be prevented with nootropic agents [21, 23, 43].

A number of nootropic compounds have been studied in detail and reported to have a cognitive activating profile [22,45] Compounds such as piracetam and choline have been used to enhance memory in normal, aged, and brain-lesioned rats [4,39]. Aniracetam, piracetam, etiracetam, oxiracetam, and pramiracetam contain the common ring, pyrrolidinone, which is related structurally to gamma aminobutyric acid. In contrast, vinpocetine (3α, 16α eburanamenine 14-carboxylic acid ethyl ester; Fig 1) is a chemically distinct compound It has been reported to increase cerebral blood flow in dog [31] and to improve cerebral metabolism as measured by changes in glucose utiliza-

[1]Requests for reprints should be addressed to Victor J DeNoble, Ph D



VINPOCETINE

FIG 1 Chemical structure of vinpocetine

tion in mice [44] Vinpocetine reportedly delays the onset of ischemic seizures in rats due to bilateral carotid occlusion [30, 32, 37, 38] and reduces hypoxia-induced lethality in mice [36] Recent open label clinical studies indicate that vinpocetine has significant cerebrovascular [46] and behavioral [40] effects in man The purpose of the present study was to compare further the preclinical activity of vinpocetine with that of other agents reported to have cognitive activating profiles A portion of this study has been reported elsewhere [13]

METHOD

Animals

Male rats of the Sprague Dawley strain were obtained from Charles River Breeding Laboratories and weighed 175–225 g at the beginning of the experiment They were housed six per cage in 26×36×25 cm stainless steel cages with food and water available. The animals were maintained on a 12-hr light/dark cycle (light on from 0700 to 1900 hr) and at a room temperature of 22–24°C with a relative humidity of 60%

Apparatus

Experimental sessions were conducted in a two-compartment shuttle box one compartment, made of clear plastic, measured 17×19×23 cm and was covered by a removable wire mesh grid, the other compartment, made of black arborite, measured 30×20×20 cm and had a floor made of 3 mm stainless steel rods spaced 2 cm apart The two compartments were separated by a solenoid-operated guillotine door (Lafayette Inst Co 85013) On either side of the door a photocell light source and a transducer were mounted with the beams parallel to the door opening A constant current shock generator (Lafayette Inst Co 82404-5) was connected to the steel rods in the darkened shock compartment through a shock scrambler. All experimental events were programmed, and responses recorded by a Rockwell Aim 65 processor located in an adjacent room

In some tests, rats were exposed to an hypoxic environment before and after passive avoidance training The hypoxia chamber was constructed from clear plastic, measured 34×23×21 cm (15 liter volume), and was continuously perfused with a gas mixture of oxygen and nitrogen The flow rate was adjusted such that the gas turnover in the chamber was 15 liters per min

Passive Avoidance Training

Passive avoidance training began by placing the rat into the clear compartment and, after a 10 sec delay, raising the guillotine door When the rat moved completely into the darkened compartment, the door was closed, and, following a 3 sec delay, a shock of 0 75 mA was applied to the grid

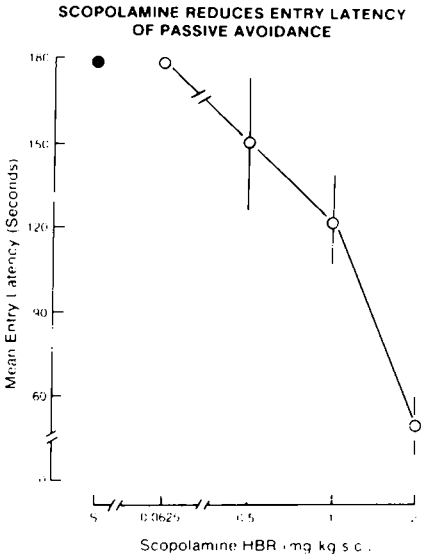


FIG 2 The latency in seconds to enter the dark compartment during retention tests is shown as a function of the scopolamine dose given 15 min before the training session The point above S represents the latency obtained following saline injections Each point is an average of data from 16 rats, and the vertical lines show the standard error of the mean

floor for 2 sec Immediately after receiving the shock the rat was removed from the dark compartment and returned to its home cage A retention test was given 24 hr later It proceeded in a manner similar to training, except that the guillotine door did not close if the rat entered the dark compartment, and the shock was not applied to the grid floor During all retention tests the rats were provided access to the dark compartment for 180 sec For memory disruption, rats were either given an injection of scopolamine HBr, or exposure to an hypoxic environment Methyl scopolamine HBr was also evaluated for its ability to disrupt memory For a scopolamine-induced disruption of retrieval, 2 0 mg/kg SC scopolamine HBr was administered 15 min prior to training For an hypoxia-induced disruption of memory, rats were exposed to a gas mixture containing known percentages of oxygen supplemented with nitrogen, 20 min before training and 20 min after training

Drug Preparation and Administration

Vinpocetine (1–300 mg/kg), vincamine (1–200 mg/kg), apovincaminic acid (1–400 mg/kg), aniracetam (1–200 mg/kg, Hoffmann LaRoche), Hydergine® (0 1–10 mg/kg, Sandoz) and pemoline (1–100 mg/kg, Abbott) were suspended in 0 5% w/v methyl cellulose and administered orally in a volume of 1 ml/kg of body weight 60 min prior to the scopolamine (Sigma) injection In tests in which rats were exposed to hypoxia, vinpocetine, vincamine, apovincaminic acid, aniracetam, Hydergine®, and pemoline were administered orally 40 min before the start of the first hypoxic episode Mecamylamine HCl (1–10 mg/kg) and (−)-nicotine (0 1–0 4 mg/kg, Bios) were dissolved in 0 9% saline and administered subcutaneously 15 min before scopolamine or exposure to hypoxia in a volume of 1 ml/kg of body weight All doses are expressed as the base substance

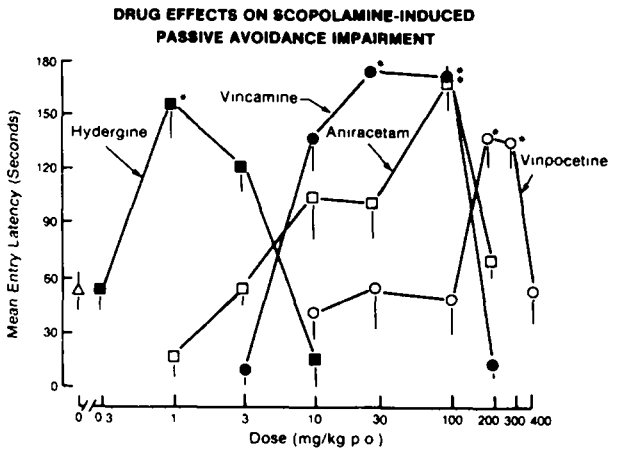


FIG 3 The latency in seconds to enter the dark compartment during the retention test is shown as a function of the dose of vinpocetine, vincamine, aniracetam, and Hydergine® administered 60 minutes prior to 2 0 mg/kg SC dose of scopolamine The point above 0 represents the average latency obtained from rats (N=512) dosed with the vehicle, the verticle line for the vehicle control group shows the standard deviation Each drug data point is a mean of data obtained from eight rats and the vertical lines show the standard error of the mean Asterisks indicate latencies that are significantly different from vehicle (Dunnett's t-test, $p<0$ 05) Mecamylamine, (−)-nicotine, pemoline and apovincaminic acid were not active in this test

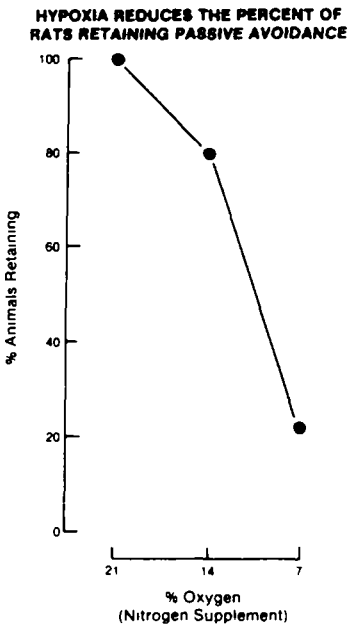


FIG 4 The percent of animals retaining the passive avoidance response 24 hr after exposure to hypoxia is shown as a function of the oxygen concentration. Points above 21% and 14% oxygen represent the mean data obtained from 16 and 32 rats, respectively, and the point above 7% oxygen shows the average of 64 rats

Data Analysis

In the tests in which scopolamine was used to disrupt memory, the means of the latencies in seconds to enter the dark compartment during the retention tests were compared for treated and vehicle control groups (N=8 per group) using Dunnett's t-test. For hypoxia-induced impairment of passive avoidance, the percentages of animals that did not enter the dark chambers during the retention test was compared for treated and vehicle control groups (N=8 per group) using Fisher's Exact Test

RESULTS

Scopolamine-Induced Deficit

The mean (±S.E.M) latency to enter the dark compartment of the passive avoidance apparatus on the training day was 20.8±4 9 sec (N=1360) On the retention day, entry latency for rats treated with saline reached 180 sec, the maximum latency of the test session. Methyl scopolamine pretreatment (1.0, 2.0, and 4.0 mg/kg SC), failed to decrease the entry latency during retention tests. However, scopolamine HBr pretreatment dose-dependently decreased entry latency (Fig 2). At a scopolamine dose of 0.0625 mg/kg SC entry latencies were not decreased. However, as the dose was increased to 0.5 and 1.0 the entry latencies decreased to 150±26 sec and 122±16 sec, respectively. Following 2.0 mg/kg SC scopolamine the mean latency to enter the dark compartment during retention test was 51.0±6.8 sec.

Pretreatment of the rats with the methyl cellulose vehicle did not alter the entry latency diminished by scopolamine (Fig 3; △ above 0) Vinpocetine at doses of 10, 30, and 100 mg/kg PO had no effect on the scopolamine-induced decrease in entry latency However, following 200 and 300 mg/kg PO vinpocetine the latency was significantly increased by 276% to 141 sec and by 264% to 138 sec, respectively (Fig. 3; open circles). At the highest dose tested (400 mg/kg PO) entry latencies were slightly below that of vehicle control rats. The scopolamine-induced decrease in entry latency was prevented when the animals were given vincamine at 10, 30, and 100 mg/kg PO; the alkaloid increased entry latency by 264, 352, and 347%, respectively A dose of 3 and 200 mg/kg PO vincamine had no effect on the scopolamine-induced decrease in entry latency (Fig. 3, filled circles).

Aniracetam also prevented the decrease in entry latency induced by scopolamine In rats treated with 10, 30, and 100 mg/kg PO of aniracetam, the entry latency was increased by 213, 203, and 327%, respectively. Entry latencies of rats treated with 200 mg/kg PO of aniracetam were below those treated with vehicle (Fig. 3; open squares). Hydergine® was also effective in preventing scopolamine-induced disruption at doses of 1 and 3 mg/kg and increased the entry latency by 309 and 241%, respectively (Fig. 3; filled squares). A 0.3 mg/kg dose of Hydergine® was not effective and 10 mg/kg of Hydergine® produced marked motor incoordination and decreased motor activity. These effects were not observed with high doses of vinpocetine, vincamine or aniracetam With all compounds that protected against the scopolamine-induced decrease in entry latency, protection was first increased as the dose was increased then decreased at higher doses.

Apovincaminic acid (1–400 mg/kg PO), the major metabolite of vinpocetine, (−)-nicotine (0.1–0 4 mg/kg SC), mecamylamine (1–10 mg/kg SC), and pemoline (1–100 mg/kg PO) did not prevent the scopolamine-induced decrease in entry latency Entry latencies for treated rats (group mean=56±8.1 sec) were not different from the grouped vehicle-treated controls.

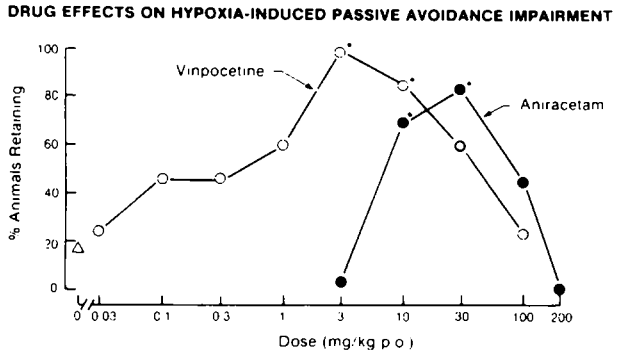


FIG 5 The percent of animals retaining the passive avoidance response (i e , not entering the dark compartment within 180 seconds) 24 hr after exposure to hypoxia is shown as a function of doses of vinpocetine and aniracetam The point above 0 represents the average number (N=300) of rats pretreated with vehicle that did not enter the dark chamber Each drug point is an average of the data from eight rats Vincamine, apovincaminic acid, Hydergine®, pemoline, mecamylamine, and (−)-nicotine were not active in this test Asterisks indicate points that are significantly different from vehicle treated rats (Fishers Exact Test, $p<0.05$)

Hypoxia-Induced Deficit

The number of animals which retained the passive avoidance response following hypoxia decreased as the oxygen concentration in the hypoxia chamber was reduced (Fig 4) That is, at 21% oxygen all rats retained the passive avoidance response. However, the number of rats demonstrating retention 24 hr after being exposed to 14% and 7% oxygen decreased to 80% and 22%, respectively

Vinpocetine prevented the hypoxia-induced retention deficit in rats (Fig 5) with the effect produced by 3 and 10 mg/kg PO differing statistically from vehicle-treated rats Despite the lack of a statistically significant protection produced by the other doses of vinpocetine (i e , 0 1, 0 3, 1, or 30 mg/kg PO), the number of animals protected from the hypnotic insult more than doubled when compared to the appropriate controls The dose of 3 mg/kg PO was the peak effective dose causing 100% of the rats to retain the passive avoidance response An increase in the number of animals retaining the response after hypoxia was also observed in rats treated with aniracetam The peak effect with aniracetam (87 5% retention) was found at a dose of 30 mg/kg PO With both compounds, the number of rats retaining the response first increased, then decreased, as the dose was increased producing an inverted U-shaped dose response curve

Apovincaminic acid (1–400 mg/kg PO), vincamine (1–200 mg/kg PO), Hydergine® (0 1–10 mg/kg PO), pemoline (1–100 mg/kg PO), (−)-nicotine (0 1–0.4 mg/kg SC), and mecamylamine (1–10 mg/kg SC) were not effective in preventing the hypoxia-induced passive avoidance retention deficit

DISCUSSION

Methyl scopolamine did not disrupt retention of a step-through passive avoidance response However, scopolamine HBr administered prior to the training of a step-through passive avoidance response impaired retention which was tested 24 hr later Since pretreatment with scopolamine HBr impaired retention and methyl scopolamine did not, it would appear that the effects of scopolamine HBr on retention are centrally mediated This effect of scopolamine on retention of passive avoidance has been reported previously [7, 24, 25] Hypoxia also impaired passive avoidance retention Previous investigations have shown that exposure to hypoxic conditions before and/or after passive avoidance training impairs retention in both mice [41] and rats [23, 33, 42] Exposure to hypoxia, both before and after training, impaired retention, and the number of animals "remembering" varied directly as a function of the chamber's oxygen concentration Our findings with both scopolamine-induced and hypoxia-induced decreases in retention of passive avoidance are in general agreement with those of others

Pretreatment with vinpocetine prevented both the scopolamine-induced (at 200 and 300 mg/kg PO) and hypoxia-induced (at 0 1 to 30 mg/kg PO) passive avoidance retention deficit in rats While the antihypoxic activity of vinpocetine has been demonstrated in rats exposed to hypobaric hypoxia [33], this is the first reporting of vinpocetine's action preventing an anticholinergic-induced memory deficit Although the mechanism by which vinpocetine exerts its effects against scopolamine or hypoxia is not known, vinpocetine has been reported to have therapeutic effects in treatment of cerebral ischemia [40] In addition, vinpocetine has been shown to increase cerebral blood flow [10] and to improve cerebral metabolism as measured by changes in glucose uptake [44] Since cholinergic agonists such as physostigmine [43] and arecoline [19] ameliorate the scopolamine amnesia in rodents, the possibility of a cholinergic influence of vinpocetine must also be considered

While vincamine was more potent than vinpocetine in preventing scopolamine-induced deficits in passive avoidance, it did not protect rats from retention impaired by hypoxic insult We corroborate an observation by Schindler and co-workers [43], who reported a similar antiscopolamine effect in mice treated with vincamine However, the action of vinpocetine and vincamine is clearly different when hypoxia was used as the memory disruptor Our results agree with those of Linee *et al* [37] who demonstrated that vincamine did not protect rats from hypobaric hypoxic-induced passive avoidance deficit

Hydergine® was the most potent agent tested in the scopolamine-impaired passive avoidance test, with significant effects seen following 1 mg/kg orally However, the ergot was inactive in the hypoxic-impairment procedure Additionally, higher doses of Hydergine® produced marked motor incoordination and ataxia Others [29] have shown Hydergine® to reverse anisomycin-induced amnesia of an approach-avoidance task in mice within a similar dose range (i e , 1 to 10 mg/kg SC)

Aniracetam, like vinpocetine, was active in preventing passive avoidance deficits induced by either scopolamine or hypoxia The aniracetam results are in general agreement with those of Cumin *et al* [11] These authors found that aniracetam (30 and 50 mg/kg PO) prevented a hypercapnia-induced deficit in acquisition of a discrete escape response in rats, and the dose-effect function formed an inverted U-shaped curve More recently, it has been shown that aniracetam or piracetam prolonged step-down passive avoidance latencies when compared with untreated control animals [49,50]

For all the nootropic agents studied, the general relationship between the dose and the retention latency is best described as an inverted U-shaped function As the dose was increased, the retention latency first lengthened, then

shortened. With Hydergine®, the highest dose tested (10 mg/kg PO) produced motor incoordination, and the decrease in retention latency may reflect the overt debilitating effects of this substance. In an ancillary experiment, vinpocetine (400 mg/kg PO), vincamine (200 mg/kg PO), and aniracetam (200 mg/kg PO), when administered at the highest dose tested in the absence of scopolamine did not result in impaired retention nor in notable overt behavioral effects The reason for the inverted U-shaped dose-effect function is unknown, but it has been repeatedly reported in studies with other compounds in different chemical classes that are thought to improve memory function [3, 8, 9, 11, 43, 48].

The nicotinic receptor agonist (−)-nicotine, up to 0 4 mg/kg SC, and the nicotinic antagonist mecamylamine, 1 to 10 mg/kg SC, had no effect on retention deficits induced by scopolamine While these doses have been shown to have behavioral effects mediated by the central nervous system [12,14], the present results corroborate previous reports that also demonstrate no effect of (−)-nicotine or mecamylamine on either step-through or step-down passive avoidance retention [15,26]. The stimulant pemoline has been shown to facilitate active avoidance performance [18] and it has been suggested that this facilitation results from a drug-induced increase in motor activity [20]. Pemoline at doses up to 100 mg/kg PO did not protect against the scopolamine-induced or hypoxia-induced retention deficit, supporting the view that pemoline does not improve memory processes.

In summary, these data support the view that vinpocetine may have cognitive activating effects as defined in models of both scopolamine-induced and hypoxia-induced memory impairment in rats. Disruption of retrieval by scopolamine is considered to result from specific antagonism of cholinergic neural substrates, whereas hypoxia-induced impairment is a more global brain insult Since vinpocetine was active in both tests, this drug may be effective in a broad range of pathological conditions which compromise memory functions

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