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Comparison of the Effects of Vinpocetine, Vincamine, and Nicergoline on the Normal and Hypoxia-Damaged Learning Process in Spontaneously Hypertensive Rats

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ABSTRACT

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Vinpocetine (Cavinton®), vincamine, and nicergoline (Sermion®) were evaluated for the ability to protect cognitive function of spontaneously hypertensive rats from the damaging effect of hypoxia. Normobaric hypoxia (6% oxygen) was applied during the acquisition of a two-way active avoidance task (3 sessions, 50 trials/session). Hypoxia decreased the percentage of conditioned avoidance responses by 50% on day 3. Vinpocetine (1.25–10 mg/kg) administered orally 60 min prior to the daily sessions did not significantly improve learning in normoxic conditions; however, it prevented hypoxia-induced learning deficit (1.25 mg/kg peak effect dose). The dose-response relationship for the compound is an inverted U-shaped curve. Vincamine (2.5–20 mg/kg p.o.) did not facilitate learning under normoxic conditions, but afforded protection against hypoxia at the 20-mg/kg dose. Nicergoline (2.5–20 mg/kg p.o.) did not increase acquisition of the normoxic avoidance response, and it also showed a moderate antihypoxic effect. Vinpocetine, and to a lesser degree vincamine and nicergoline—drugs useful in the therapy of cognitive disturbances following cerebral ischemic-hypoxic states—proved effective in the prevention of a hypoxia-induced learning deficit.

Key words: cognitive enhancer, antihypoxic, two-way active avoidance

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INTRODUCTION

Conditions that reduce energy supply to the brain, such as hypoxia and cerebral ischemia, impair learning and memory processes [Jensen and DeFine Olivarius, 1980; Clincke and Wauquier, 1984]. These experimental conditions represent the animal models of human cognitive disorders caused by transitional or permanent hypoxic states, e.g., senile ischemic cerebrovascular disease. Compounds possessing cerebral-blood-flow-increasing and/or cerebral-metabolism-improving activities have favorable effects in both animals [Schindler et al., 1984] and man [Blaha, 1979; Weitbrecht, 1983].

Two eburnamenine compounds, vinpocetine (Cavinton®) and vincamine, and the ergoline derivative nicergoline (Sermion®) have both the aforementioned pharmacologic actions. According to the literature, they are effective in the treatment of age-related cerebrovascular disease [Hadjiev and Yancheva, 1976; Marolda et al., 1978; Arrigo et al., 1982; Hagstadius et al., 1984; Otomo et al., 1985]. Several preclinical studies demonstrate the favorable antihypoxic, memory-enhancing characteristics of these compounds [Paul and Chandra, 1979; Groó et al., 1980; Pálosi et al., 1980; Truchaud and Moriniere, 1980; Kiss et al., 1982; Milanova et al., 1983; DeNoble et al., 1986; King and Narcavage, 1986].

The purpose of the present study was to compare the effect of vinpocetine, vincamine, and nicergoline on learning in rats, under both normoxic and hypoxic conditions. In our experiments, we have used spontaneously hypertensive (SH) rats, as this strain is reported sensitive to stressful stimuli [McCarty and Kopin, 1979; Krauchi et al., 1983], and, according to our unpublished observations, SH rats show greater hypoxic vulnerability than do normotensive Wistar rats.

MATERIALS AND METHODS

Animals

Male Wistar-derived spontaneously hypertensive rats (bred at Gedeon Richter Ltd.; blood pressure 180–210 mmHg) weighing 140–160 g were used. The animals were housed six per cage with food and water available ad libitum. The rats were maintained on a 12-hr light/dark cycle, at a room temperature of 20–22°C, and at 50–60% relative humidity.

Drugs

Vinpocetine and vincamine (Gedeon Richter Ltd., Hungary) were dissolved in 2% ascorbic acid, and nicergoline (synthesized at Gedeon Richter Ltd., Hungary) was dissolved in 1% tartaric acid, diluted to the required volume by distilled water, and the pH was adjusted to 4.5 with NaOH. All drugs were administered daily in a volume of 0.5 ml/kg body weight p.o. 60 min prior to daily test sessions at doses of 1.25 (only vinpocetine), 2.5, 5.0, 10.0, and 20.0 (vincamine and nicergoline) mg/kg. Vehicle-treated rats served as controls.

Apparatus

Experimental sessions were conducted in six microprocessor-programmed, two-compartment (20×26 × cm each) shuttle boxes (VKI, Hungary). There was a 10×8-cm opening between the two compartments, and a photocell light source and transducer sensed the crossings between the compartments. An intensive light flashing with a 1-Hz frequency served as the conditioning stimulus, and a 0.8-mA, 0.2-sec footshock administered through the grid floor of the compartment was used as the unconditioned stimulus. All responses were recorded by the microprocessor.

Active Avoidance Training

Active avoidance training was conducted during 50 daily trials for 3 days. One trial consisted of a 15-sec intertrial interval, a 15-sec conditioned stimulus, and a 10-sec footshock.

The animal could terminate the trial by crossing into the adjacent compartment during the light stimulus—in this case it was recorded as conditioned avoidance response (CAR)—or by escaping the footshock (recorded as unconditioned response). Escape failures were also recorded. After the end of the daily session the animals were removed from the shuttle box and returned to their home cage.

Normobaric hypoxia was induced in three shuttle boxes by a 200-liter/hr box perfusion of pressurized nitrogen and oxygen in a ratio giving 6% oxygen content in the inspired air. Daily test sessions were begun after a 20-min equilibration and normobaric hypoxia was maintained during the period of acquisition.

Statistics

Using Dunnett's t-test, a comparison was made between treated and vehicle control groups ($n = 6$ per group) with respect to the percentage of avoidance responses and escape failures during every three session. The differences were considered significant if $P < 0.05$.

RESULTS

Effect on Acquisition

On the first day of learning (i.e., session 1), vinpocetine, vincamine, and nicergoline did not alter acquisition; the higher doses of vinpocetine and nicergoline slightly, but not significantly, decreased the percentage of escape failures (Table 1).

In the second session (day 2), the 5.0- and 10-mg/kg doses of vinpocetine, as well as 10 mg/kg of vincamine and 20 mg/kg of nicergoline, produced some improvement in learning. All three drugs lowered the incidence of escape failures (Table 1).

On day 3, none of the treated groups showed considerably better performance than the control group, except the one treated with 1.25 mg/kg vinpocetine. Here, also, the percentage of escape failures decreased compared to the control in every treated group (Table 1).

Effect on Hypoxia-Induced Learning Deficit

Lowering the oxygen contents of inspired air to 6% impaired acquisition of the avoidance response, and the difference between the performance (percentage of avoidance responses) of animals kept under normoxic and hypoxic conditions was significant on day 3 (69.2% and 38.0% CAR, respectively; Fig. 1). Hypoxia increased the incidence of escape failures, too.

In the first session, only 1.25 mg/kg of vinpocetine prevented the hypoxia-induced learning deficit; the other doses and compounds did not increase the number of avoidance responses. However, the low doses (1.25 or 2.5 mg/kg) of the drugs and 20 mg/kg vincamine lessened the number of escape failures (Table 2).

On day 2, vinpocetine in the dose range of 1.25–5.0 mg/kg was effective—its effect decreased at higher doses. Vincamine at a dose of 20 mg/kg significantly improved the performance of animals. Nicergoline showed the most favorable effect at its lowest applied dose of 2.5 mg/kg. The number of escape failures was similar to that of the previous day (Table 2).

In the third session (day 3), vinpocetine exerted a significant, pronounced antihypoxic activity in the 1.25–10-mg/kg dose range. Here, the performance of animals reached that of the rats trained under normoxic conditions. Specifically, the 1.25-mg/kg-vinpocetine dose group showed a higher percentage of avoidance than the control, which may be an indication of a slight acquisition-improving effect of this dose of vinpocetine. The highest dose of vincamine (20 mg/kg) also protected animals from hypoxia. Nicergoline afforded some protection against hypoxia, but it did not reach a level of significance. Doses of 1.25–10

TABLE 1. Effect of Vinpocetine, Vincamine, and Nicergoline on Normoxic Learning in SH Rats During Daily Acquisition Sessions for 3 Days

			1st session		2nd session		3rd session	
Compound	Dose (mg/kg p.o.)	N	% of CAR ($\bar{x} \pm SE$)[a]	% of EF ($\bar{x} \pm SE$)[b]	% of CAR ($\bar{x} \pm SE$)[a]	% of EF ($\bar{x} \pm SE$)[b]	% of CAR ($x \pm SE$)[a]	% of EF ($\bar{x} \pm SE$)[b]
Vehicle control		20	36.2 ± 2.7	5.2 ± 4.2	57.6 ± 4.9	8.4 ± 6.0	69.2 ± 4.4	7.4 ± 3.8
Vinpocetine	1.25	6	39.0 ± 7.5	4.4 ± 1.7	75.0 ± 11.7	0	83.0 ± 3.8	0.4 ± 0.3
	2.5	6	19.6 ± 3.5	4.6 ± 2.8	46.6 ± 8.4	1.4 ± 1.3	68-6 ± 11.3	0
	5.0	6	32.4 ± 6.8	1.4 ± 0.8	75.0 ± 4.2	0	76.0 ± 6.2	0.4 ± 0.3
	10.0	6	30.6 ± 8.1	3.0 ± 1.4	77.4 ± 7.2	1.0 ± 1.0	68.0 ± 6.7	0
Vincamine	2.5	6	23.6 ± 6.1	1.6 ± 0.6	61.0 ± 8.2	0	76.8 ± 2.6	0
	5.0	6	21.0 ± 5.6	1.4 ± 0.8	62.6 ± 8.2	0	45.0 ± 6.3	0
	10.0	6	23.4 ± 7.3	8.4 ± 5.0	73.0 ± 4.3	0	69.0 ± 5.9	3.5 ± 3.5
	20.0	6	25.6 ± 4.1	4.2 ± 1.5	55.6 ± 8.0	0	42.0 ± 5.2	3.4 ± 2.9
Nicergoline	2.5	6	25.0 ± 7.6	7.0 ± 6.2	33.0 ± 6.6	0	67.6 ± 3.0	0
	5.0	6	35.0 ± 5.0	0.4 ± 0.3	62.4 ± 5.5	0	68.4 ± 3.0	0
	10.0	6	44.4 ± 9.8	0.4 ± 0.3	57.4 ± 14.0	0.6 ± 0.7	48.6 ± 10.9	3.0 ± 2.6
	20.0	6	32.6 ± 8.6	1.0 ± 0.7	69.4 ± 5.3	0	61.0 ± 6.5	0.6 ± 0.7

[a]% of CAR = percentage of conditioned avoidance responses.
[b]% of EF = percentage of escape failures.

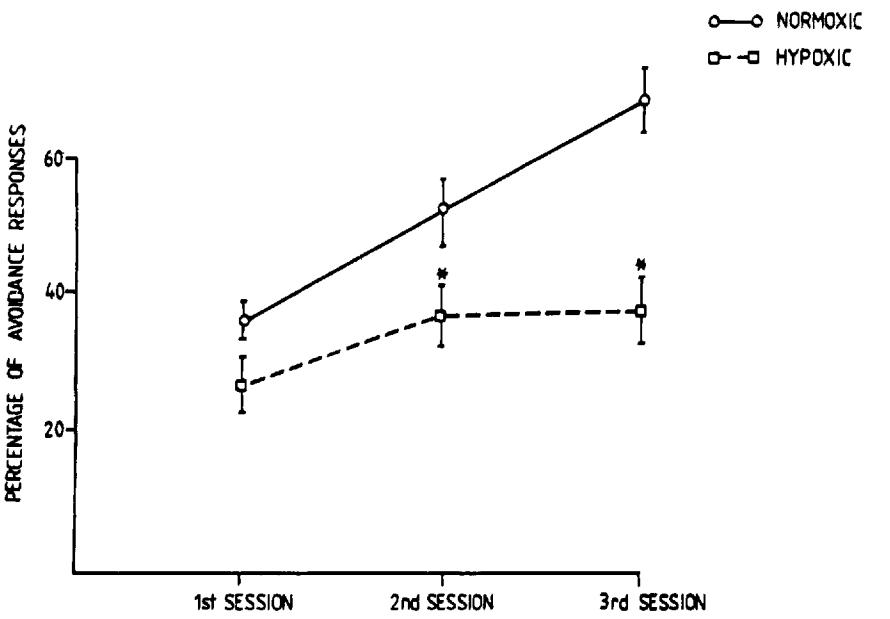

Fig. 1. Effect of daily normobaric hypoxia (6% O_2) on the acquisition of conditioned avoidance response (CAR) in spontaneously hypertensive (SH) rats. Each point represents the mean (+ SE) of the number of CAR's of 20 rats in the percentage of total responses. Asterisks above the points indicate percentages that are significantly different from the performance (CAR %) of normoxic vehicle-treated SH rats (Dunnett's t-test; $P < 0.05$).

mg/kg of vinpocetine, 2.5 and 20 mg/kg of vincamine, and 2.5, 10, 20 mg/kg of nicergoline decreased the ratio of escape failures (Table 2).

In Figures 2–4, the effect of vinpocetine, vincamine, and nicergoline on acquisition of SH rats under normoxic and hypoxic conditions is illustrated graphically.

DISCUSSION

In the present study, a model of hypoxia-induced cognitive impairment in rats has been used to evaluate the pharmacologic effects of selected compounds (vinpocetine, vincamine, nicergoline) that are clinically effective in the treatment of memory disturbances following cerebral ischemia-hypoxia [Hadjiev and Yancheva, 1976; Marolda et al., 1978; Arrigo et al., 1982; Hagstadius et al., 1984; Otomo et al., 1985].

On the basis of results from our pilot studies, Wistar-derived spontaneously hypertensive (SH) rats were used in our experiments for the reason that this genetic line demonstrated a lower level of acquisition in some learning tasks [Friedman and Weiss, 1974; Rosecrans and Adams, 1976; Sutterer et al., 1980; Friedman et al., 1981]. This has been attributed to the animals' decreased reaction to aversive stimuli and decreased general adaptative ability [McCarty and Kopin, 1979; Kräuchi et al., 1983; Gentsch et al., 1987]. The former observation was corroborated in our experiments, where SH rats displayed poor learning ability in the two-way active avoidance task when compared to the individuals of the Hannover Wistar strain. A further and very important difference between the two strains is, according to our own behavioral results and to existing literature demonstrating increased peripheral responses to hypoxia [Meerson et al., 1980; Hagberg et al., 1983], the reduced tolerance of SH

TABLE 2. Effect of Vinpocetine, Vincamine, and Nicergoline on Hypoxia-Induced Learning Deficit in SH Rats During Daily Acquisition Sessions for 3 Days

			1st session		2nd session		3rd session	
Compound	Dose (mg/kg p.o.)	N	% of CAR ($\bar{x} \pm SE$)[a]	% of EF ($\bar{x} \pm SE$)[b]	% of CAR ($\bar{x} \pm SE$)[a]	% of EF ($\bar{x} \pm SE$)[b]	% of CAR ($\bar{x} \pm SE$)[a]	% of EF ($\bar{x} \pm SE$)[b]
Vehicle control		20	32.6 ± 2.7	5.2 ± 4.2	57.6 ± 4.9	8.4 ± 6.0	69.2 ± 4.4	7.4 ± 3.8
Hypoxic vehicle control		20	26.4 ± 4.4	19.8 ± 10.2	37.0 ± 4.6*	20.6 ± 9.1	38.0 ± 5.0*	14.6 ± 8.1
Vinpocetine	1.25	6	45.4 ± 6.3	2.0 ± 1.0	80.0 ± 4.8**	0	84.4 ± 4.8**	0
	2.5	6	26.4 ± 5.0	2.0 ± 1.3	53.6 ± 5.5	0.7 ± 0.7	58.6 ± 9.8	0.3 ± 0.3
	5.0	6	29.2 ± 8.5	6.3 ± 6.3	58.6 ± 11.0**	5.5 ± 5.5	63.6 ± 6.9	6.0 ± 6.0
	10.0	6	24.2 ± 7.7	19.6 ± 7.4	50.0 ± 12.1	9.6 ± 8.9	63.4 ± 8.6**	3.6 ± 2.0
Vincamine	2.5	6	32.8 ± 5.4	4.6 ± 3.4	44.4 ± 7.5	0.6 ± 0.7	40.4 ± 4.9	0.6 ± 0.7
	5.0	6	22.0 ± 6.5	10.6 ± 7.6	26.6 ± 6.7	13.6 ± 7.3	28.0 ± 7.8	10.4 ± 8.6
	10.0	6	14.0 ± 4.3	22.6 ± 8.8	18.6 ± 1.3	10.4 ± 4.2	26.6 ± 7.4	18.0 ± 8.3
	20.0	6	35.0 ± 3.9	3.2 ± 2.6	72.4 ± 4.1**	0	82.0 ± 5.1**	0
Nicergoline	2.5	6	20.4 ± 6.7	5.6 ± 3.9	54.6 ± 5.4	1.4 ± 1.4	52.4 ± 6.0	1.0 ± 1.0
	5.0	6	16.0 ± 10.5	36.6 ± 13.3	26.0 ± 1.2	17.4 ± 7.1	33.4 ± 8.6	13.4 ± 8.4
	10.0	6	35.0 ± 5.0	14.0 ± 14.0	27.4 ± 2.8	28.0 ± 14.1	54.0 ± 6.2	2.6 ± 0.7
	20.0	6	22.0 ± 7.0	16.6 ± 7.3	33.4 ± 7.7	6.0 ± 4.1	44.6 ± 6.6	0.6 ± 0.7

[a]% of CAR = percentage of avoidance responses.
[b]% of EF = percentage of escape failures.
*$P < 0.05$ (compared to vehicle control).
**$P < 0.05$ (compared to hypoxic vehicle control).

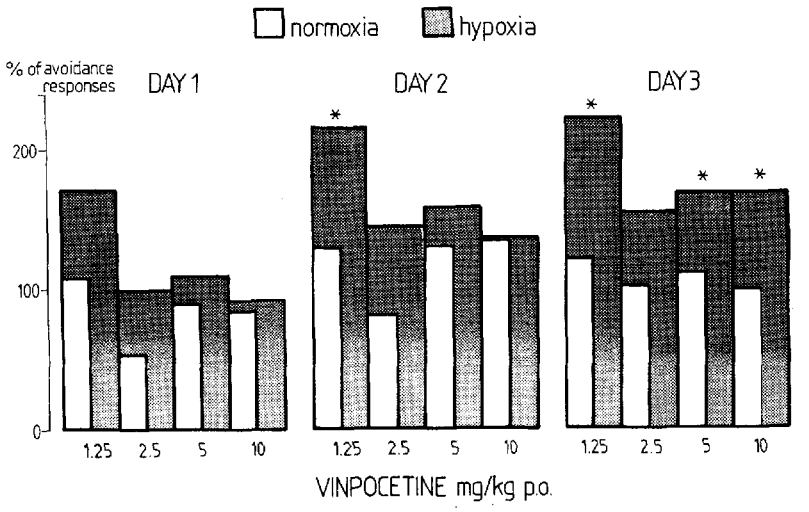

Fig. 2. Alteration of the number of avoidance responses under normoxic and hypoxic conditions in SH rats (n = 6) following daily vinpocetine treatment. Avoidance responses (group means) are presented in the percent of daily normoxic and hypoxic control values, respectively. Asterisks above the bars indicate percentages that are significantly different from the performance (CAR %) of hypoxic vehicle-treated rats (Dunnett's t test; $P < 0.05$).

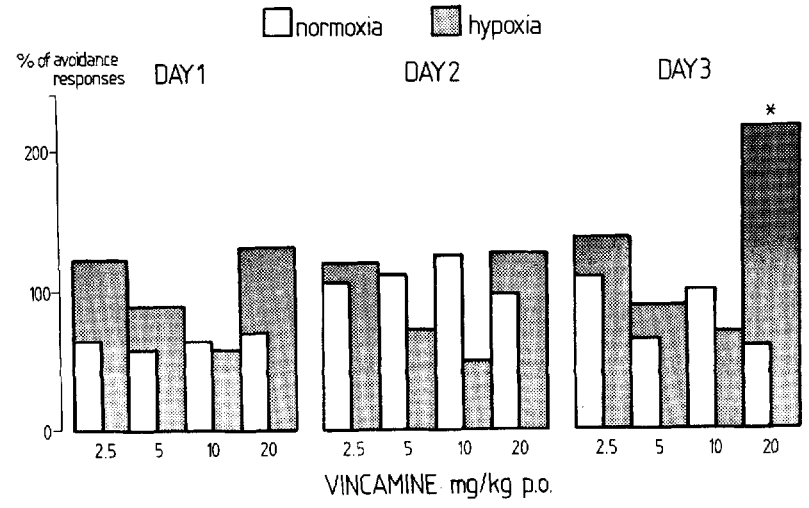

Fig. 3. Alteration of the number of avoidance responses under normoxic and hypoxic conditions in SH rats following daily vincamine treatment. Conventions for data presentation are the same as in Figure 2.

rats to hypoxic conditions. Thus, these animals seemed to be suitable for experiments that measure cognitive function impaired by hypoxia.

A learning deficit was induced by normobaric hypoxia (6% oxygen content in the inspired air) in a two-way active avoidance paradigm. Our results in general are in good agreement with those of Saligaut et al. [1981], where the acquisition of a conditioned avoidance response was impaired by 300 torr hypobaric hypoxia (8% oxygen content).

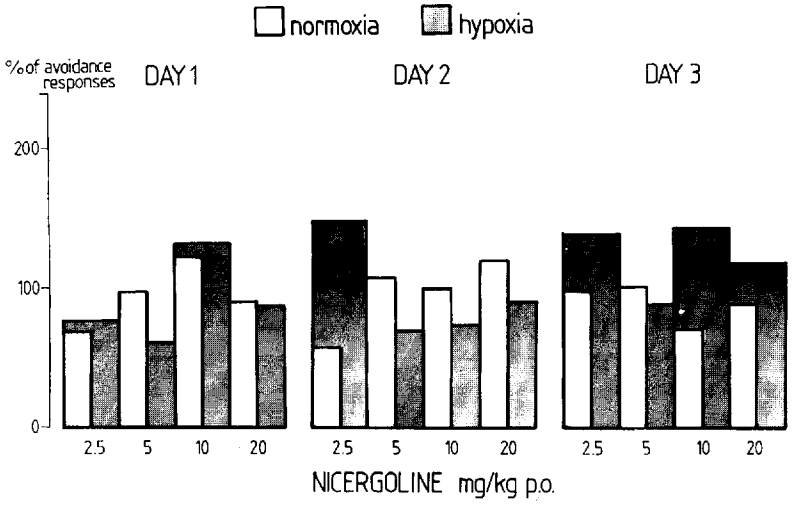

Fig. 4. Alteration of the number of avoidance responses under normoxic and hypoxic conditions in SH rats following daily nicergoline treatment. Conventions for data presentation are the same as in Figure 2.

Similarly to their results, in our experiments the learning deficit was most pronounced on the third day of training; the performance of hypoxic animals was approximately half that of normoxic rats.

Comparing the effects of vinpocetine, vincamine, and nicergoline on learning under normoxic and hypoxic conditions the following conclusions may be drawn. Vinpocetine does not significantly improve learning of a conditioned avoidance paradigm under normoxic circumstances (except by decreasing the number of escape failures); however, it exerts an acquisition-enhancing effect under hypoxic conditions. The favorable activity of the compound is not an aspecific, acquisition-accelerating effect. The effectivity of vinpocetine increases with time—that is, it has the most significant effect on the third day. The lowest dose (1.25 mg/kg) proved to be the most effective and the higher doses less active. Thus, the dose-response relationship is an inverted U-shaped curve which is frequently obtained with compounds reportedly improving cognitive functions [Cumin et al., 1978; Butler et al., 1981; Schindler et al., 1984; DeNoble et al., 1986]. According to our present results and to the literature [DeNoble et al., 1986], the protective effect of vinpocetine appears in lower doses in situations where higher nervous system functions, memory, or learning are disrupted by hypoxia rather than under lethal hypoxic conditions (i.e., asphyxia, ischemia, hypobaric, hemic hypoxia). In the latter cases, the peak effect dose of vinpocetine is 10–20 mg/kg i.p. [Groó et al., 1980; Milanova et al., 1983; King and Narcavage, 1986; King, 1987], while the compound protects cognitive function against hypoxic damage in the 1.25–3.0-mg/kg oral dose range.

Since vinpocetine's protective activity against hypoxia-induced memory failure has been demonstrated and assessed only in situations where hypoxia was used as a memory disrupting agent before or after training in a one-trial passive avoidance task [DeNoble et al., 1986], we compared its effect to that of vincamine and nicergoline, in our experimental paradigm where hypoxia was applied during the whole period of learning.

Vincamine, similarly to vinpocetine, did not improve learning in SH rats, but it afforded protection against hypoxia-induced learning deficit at the highest (20 mg/kg) dose. This limited antihypoxic effect is in contrast with some reports [Linee et al., 1978; DeNoble et al., 1986] where vincamine did not protect rats from hypobaric hypoxia-induced passive avoidance deficit, but this difference may be explained by different test conditions.

Nicergoline did not significantly facilitate two-way active avoidance learning under normoxic conditions (except some improvement on day 2), contrary to some data in the literature where it improved the learning process in an operant conditioning task [Paul and Chandra, 1979]. The compound showed limited antihypoxic effect when the acquisition ability of animals was inhibited by normobaric hypoxia. It is known that nicergoline promotes the posthypoxic recovery of neurons, but does not modify brain metabolism during the period of hypoxia [Benzi et al., 1979; Moretti, 1979]. Our nonsignificant results with this well-known cognitive enhancer may follow from the fact that under the present test conditions (i.e., treatment prior to daily hypoxia) nicergoline was not able to exert a protective effect.

The possibility may arise that the tested compounds lower the blood pressure of SH rats, either under normoxic conditions or in hypoxia, and blood pressure lowering may be the basis of the protective effect. According to our unpublished observations, the blood pressure of SH rats decreases approximatively 10–20% following hypoxia. Vinpocetine, vincamine, and nicergoline do not lower the blood pressure of SH rats under normoxic conditions, and do not influence the hypoxia-induced fall of blood pressure. Our observations are in accord with those of Friedman et al. [1981]. They reported that the impaired acquisition ability of SH rats correlate with predisposition to hypertension, but not with high blood pressure per se. It was hypothesized that common inherited characteristics may be responsible for both the behavioral and cardiovascular phenotypes in the rats sensitive to hypertension.

Under the normobaric hypoxic conditions applied in our learning model, vinpocetine had the most significant antihypoxic activity. The exact mechanism of action of the compound is not yet determined, but it has been reported that, in addition to a cerebral blood flow-increasing effect [Kárpáti and Szporny, 1976], it improves cerebral glucose uptake [Shibota et al., 1982], and increases the turnover of norepinephrine in brain [Kiss et al., 1982]. These effects of vinpocetine may contribute to its activity against hypoxia-induced learning deficit in SH rats.

Vinpocetine, and to a lesser extent vincamine and nicergoline, three compounds successfully used in the therapy of memory disturbances following cerebral ischemic-hypoxic states, proved to be effective in the prevention of normobaric hypoxia-induced learning deficit in a two-way active avoidance task in SH rats. This test situation may in some respects resemble the functional consequences of human dementia states deriving from impaired oxygen supply of brain areas (e.g., multiinfarct dementia), and compounds exerting beneficial activity in this animal model may be useful in the treatment of cognitive disorders of ischemic-hypoxic etiology.

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