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Effects of Vinpocetine in Scopolamine-Induced Learning and Memory Impairments

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ABSTRACT

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Scopolamine-induced memory dysfunctions are related to reduced cholinergic transmission. In our experiments scopolamine (3.0 mg/kg i.p.) inhibited acquisition and induced retrograde amnesia in a one-trial step- through passive avoidance task in mice. We have studied the effect of vinpocetine (Cavinton^R), in the amnesic states mentioned above compared to that of vincamine, nicergoline (Sermion^R), and papaverine, to assess its activity on learning and memory processes impaired by scopolamine. Vinpocetine decreased the disrupting effect of scopolamine on acquisition and prevented and restituted the memory loss with 21.0 and 7.0 mg/kg i.p. peak effect dose, respectively. It facilitated the recall of memory traces damaged by scopolamine. Vincamine (3.5–63.7 mg/kg i.p.) showed a favorable effect in two of the four tests (reversal of amnesia and recall). Nicergoline (5–40 mg/kg i.p.) exerted moderate activity, and papaverine (10–40 mg/kg i.p.) was ineffective in the situations tested. Our findings indicate that vinpocetine directly or indirectly influences the cholinergic system, which may explain its previously reported beneficial effect in electroconvulsive shock- and hypoxia-induced experimental amnesic states, and its therapeutic activity in human mental and cognitive disorders.

Key words: amnesia, memory, learning, passive avoidance

INTRODUCTION

Vinpocetine (Cavinton^R, manufactured by Chemical Works of Gedeon Richter, Ltd.) is an indole derivative possessing an antihypoxic effect. According to the results of previous

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examinations the compound exerts antihypoxic activity in severe hypoxic states, namely, in asphyxic anoxia and hypobaric, anemic, and cytotoxic hypoxias [Groó et al., 1980; Milanova et al., 1983], and has beneficial effect in retrograde amnesic states induced by electroconvulsive shock (ECS), or hypobaric hypoxia (HH), when these treatments are applied following one-trial passive avoidance training [Kiss et al., 1982; DeNoble et al., 1986].

We tried to explain this antihypoxic activity of vinpocetine by its effect on cerebral transmitter mechanisms, as according to biochemical investigations, it accelerates the turnover rate of catecholamines, especially that of noradrenaline [Kiss et al., 1983].

It is well known, that acetylcholine deficiency plays an important role in the etiology of Alzheimer's disease [Gottfries, 1985]. To study the effect of vinpocetine on acetylcholine (ACh) metabolism and assess its possible use in the therapy of Alzheimer disease we have applied a model, in which in a one-trial step-through passive avoidance task the memory functions of mice were impaired by scopolamine, an anticholinergic agent. The antiamnesic effect of vinpocetine was compared to that of vincamine, nicergoline (Sermion^R), and papaverine as reference compounds, as these drugs all possess therapeutic activity in cerebral hypoxic states of different etiology, but exert their effect through dissimilar mechanisms of action.

MATERIALS AND METHODS

Vinpocetine (VP, Chem. Works of Gedeon Richter, Ltd.) and vincamine (VA, Chem.Works of Gedeon Richter) were dissolved in 1% ascorbic acid, nicergoline (NG) in 0.5% tartaric acid, and the solutions were neutralized (pH = 5.0) by 1 N NaOH and diluted to the required concentration by physiological saline. Papaverine (PAP, Chinoin) and scopolamine (SC, Sigma) were dissolved in physiological saline. The solutions were administered intraperitoneally (i.p.) in a volume of 10 ml/kg body weight. In every treatment sequence (see Fig. 1) the control groups received placebo (the solvent of the appropriate compound) at the same time that the treated groups were injected with the drugs and physiological saline instead of scopolamine. The scopolamine groups were treated by the solvents at the appropriate moment, and by scopolamine. Vinpocetine was administered in doses of 3.5, 7.0, 21.0, and 63.0 mg/kg; vincamine in doses of 3.5, 7.1, 21.3, and 63.7 mg/kg; nicergoline in doses of 5.0, 10.0, 20.0, and 40.0 mg/kg; and papaverine in doses of 10.0, 20.0, and 40.0 mg/kg; all doses were administered i.p. Scopolamine was given in a 3.0-mg/kg i.p. dose. Lati: CFLP mice of both sexes weighing 18–21 g were used for the experiments. Each dose group consisted of 20 animals (10 males and 10 females).

The one-trial step-through passive avoidance test described by Essman and Alpern [1964] was applied. Mice were placed on a platform connected to the dark test box. When the mice entered the dark area, an electric footshock (1.5 mA, 0.3 sec) was given as unconditioned stimulus. Twenty-four hours later the animals were once again placed on the platform and the percentage of mice that had not entered the dark area in 60 sec was measured (i.e., the percentage of correct responses).

Vinpocetine, reference compounds, and scopolamine were administered in the sequences shown in Figure 1.

RESULTS

Following one-trial learning ~70% of the animals avoided entering the box at retesting (C in Figs. 2–5). Scopolamine administered 60 min prior to learning inhibited acquisition (Fig. 2, SC). When given 120 min after learning, scopolamine induced retrograde amnesia (Figs. 3–5, SC); only ~20% of mice remembered the footshock stimulus and did not enter at retesting 24 hr later.

Vinpocetine was the only compound that exerted a beneficial effect on the learning process impaired by scopolamine (Fig. 2). Its effect was dose-dependent, and following the

1. Prevention of anterograde amnesia

$$T \xrightarrow{30'} Sc \xrightarrow{60'} L \xrightarrow{24^h} R$$

2. Prevention of retrograde amnesia

$$L \xrightarrow{60'} T \xrightarrow{60'} Sc \xrightarrow{24^h} R$$

3. Restitution of retrograde amnesia

$$L \xrightarrow{120'} Sc \xrightarrow{60'} T \xrightarrow{24^h} R$$

4. Influence on retrieval process

$$L \xrightarrow{120'} Sc \xrightarrow{23^h} T \xrightarrow{60'} R$$

Fig. 1. Treatment schedules. T = treatment; Sc = scopolamine; L = learning; R = retesting.

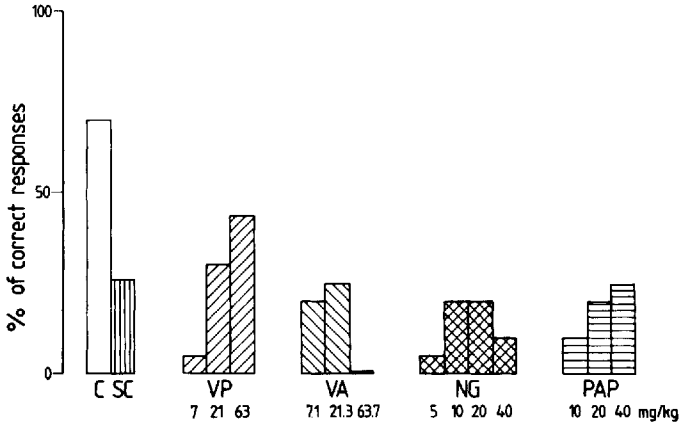

Fig. 2. Prevention of anterograde amnesia. Scopolamine (SC, 3.0 mg/kg i.p.) was given 30 min following i.p. treatment by test compounds, and 90 min prior to training; animals were retested 24 hr later. C = control, SC = scopolamine, VP = vinpocetine, VA = vincamine, NG = nicergoline, PAP = papaverine.

administration of the highest dose (63.0 mg/kg), the performance of animals approached that of the control group.

In the prevention of retrograde amnesia vinpocetine showed a significant effect (Fig. 3, VP). Even in the lowest dose (7.0 mg/kg) it doubled the percentage of nonamnesic animals, and following the administration of higher doses (21.0 and 63.0 mg/kg) more mice retained the memory of footshock than in the control group.

Vinpocetine effectively restituted retrograde amnesia induced by scopolamine (Fig. 4, VP). In the lowest dose (3.5 mg/kg) it doubled the percentage of nonamnesic animals, when compared to control, and after the administration of higher doses the percentage of remembering animals did not differ from the control value.

Vinpocetine had a beneficial effect on the retrieval process in a test situation, in which the consolidation of memory had been disturbed by scopolamine, and VP was administered 1 hr before retesting. A total of 50–60% of treated mice showed passive avoidance, in contrast to 23% in the control group (Fig. 5, VP).

Among the reference compounds vincamine (VA) had the most significant effect, but it reached that of vinpocetine only in the experimental situation that tested the influence on retrieval process. Thus VA facilitated the memory of animals damaged by scopolamine even

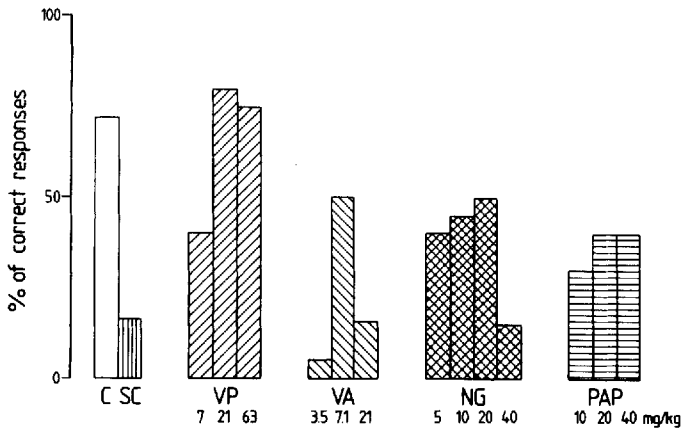

Fig. 3. Prevention of retrograde amnesia. Scopolamine (SC, 3.0 mg/kg i.p.) was given 120 min after training and 60 min after i.p. treatment by test compounds; animals were retested 24 hr later. C = control, SC = scopolamine, VP = vinpocetine, VA = vincamine, NG = nicergoline, PAP = papaverine.

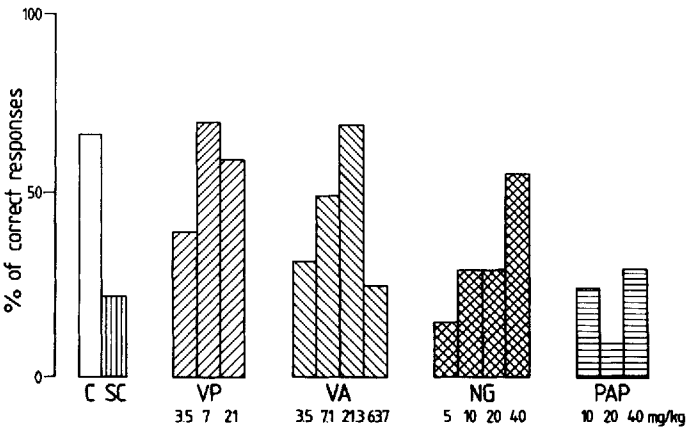

Fig. 4. Reversal of retrograde amnesia. Scopolamine (SC, 3.0 mg/kg i.p.) was given 120 min after training and 60 min before i.p. treatment by test compounds; animals were retested 24 hr later. C = control, SC = scopolamine, VP = vinpocetine, VA = vincamine, NG = nicergoline, PAP = papaverine.

at its lowest tested dose (3.5 mg/kg) (Fig. 4, VA). In the prevention of anterograde and retrograde amnesia VA had a negligible effect (Figs. 2 and 3, VA), but the 21.3-mg/kg dose successfully restituted amnesia induced by scopolamine (Fig. 4, VA).

Nicergoline exerted only moderate effect in all test situations. In the prevention of retrograde amnesia the percentge of remembering animals reached 50% following the administration of 20 mg/kg (Fig. 3, NG). The compound had some beneficial effect on the retrieval process disturbed by scopolamine (Fig. 5, NG). Papaverine had no considerable effect on learning or memory processes impaired by scopolamine.

DISCUSSION

The central cholinergic system plays a determinant role in the storage and retrieval of information. Experimental insults influencing ACh metabolism induce impairments in memory functions. It is possible that the disruptive effect of ECS is mediated through the cholinergic system [Davis et al., 1971], and ACh metabolism is particularly vulnerable to hypoxia, too

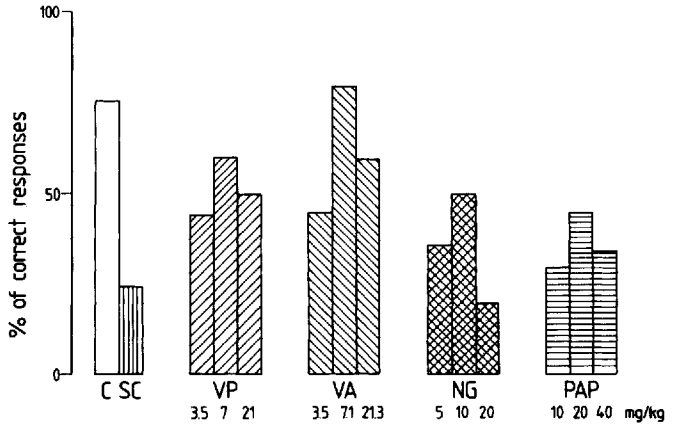

Fig. 5. Influence of test compounds on the retrieval process. Scopolamine (SC, 3.0 mg/kg i.p.) was given 120 min after training; the animals were treated by the test compounds 60 min prior to retesting performed 24 hr following training. C = control, SC = scopolamine, VP = vinpocetine, VA = vincamine, NG = nicergoline, PAP = papaverine.

[Gibson et al., 1978; Gibson and Duffy, 1981]. According to Drachman [1978] hypoxia and compounds with cholinergic receptor antagonistic characteristics produce similar behavioral symptoms.

Scopolamine produces deficits closely mimicking the pathological ischemic or natural age-related damage of memory. Bartus et al. [1982] pointed out that scopolamine-induced memory impairments resemble those seen in Alzheimer disease. In animal studies scopolamine treatment has been shown to inhibit the acquisition in several learning situations [Meyers et al., 1964; Carlton and Vogel, 1965; Jarvik and Kopp, 1967; Flood and Cherkin, 1986; Beatty et al., 1986], particularly in the case of passive avoidance [Meyers, 1965; Meyers and Lazarus, 1967; Bohdanecky and Jarvik, 1967; Calhoun and Smith, 1968; DeNoble et al, 1986]. In humans scopolamine produces amnesic effects both in experimental and clinical situations [Drachman and Leawitt, 1974; Drachman, 1977; Petersen, 1977].

Our findings verified the learning and memory impairing activity of scopolamine. The compound given prior to training inhibited the acquisition of passive avoidance (anterograde amnesia) and induced retrograde amnesia when administered in the first 2 hr after learning, a time at which the memory trace is still vulnerable.

In investigating the effect of vinpocetine in different scopolamine-induced amnesic states, we have chosen vincamine, nicergoline, and papaverine as reference compounds, as these drugs all possess some therapeutic activity in cognitive disorders of different etiology, but exert their effect through different mechanisms. According to our unpublished data the tested compounds in the applied dose range do not induce sedation or other side effects that might result in aspecific memory-improvement or impairment. None of the drugs influence passive avoidance in itself.

Vinpocetine increases cerebral blood flow [Imamoto et al., 1984], has a protective effect in cerebral ischemia [Biró et al., 1976; Kakihana et al., 1982; Nagaoka et al., 1984; King et al., 1985] and hypoxia [Kárpáti and Szporny, 1976; Groó et al., 1980; Milanova et al., 1983; DeNoble et al., 1986], influences favorably the energy and oxygen supply of brain areas damaged by hypoxia [Kárpáti and Szporny, 1976], and improves glucose utilization of whole brain [Shibota et al., 1982]. The compound is a potent inhibitor of cerebral phosphodiesterase, inducing a rise in cyclic AMP [Rosdy et al., 1976] and cyclic GMP contents [Hagiwara et al., 1984].

Vincamine, similarly to vinpocetine, increases cerebral blood flow [Depresseux, 1977; Hagstadius et al., 1984], stimulates neuronal metabolism [Blanquet et al., 1969], and increases

the oxygen and glucose consumption of the brain [Tesseris et al., 1975]. It exerts antihypoxic activity in various circumstances [Groó et al., 1980; Milanova et al., 1983; Marzo et al., 1982].

Nicergoline, besides producing a moderate vasodilating and central blood flow increasing effect [Bienmüller and Betz, 1972; Suchowsky and Pergrassi, 1974; Benzi et al., 1973], is able to afford a certain degree of protection to the brain against the effects of hypoxia. Nicergoline reportedly increases the oxygen consumption of the brain [Benzi et al., 1971] and the glucose uptake depressed by hypoxia [Benzi et al., 1972].

Papaverine is a classical myogenic vasodilator increasing cerebral blood flow [Rossignol and Ebigwei-Ibru, 1980] and cerebral tissue pO_2 [Nikolov and Leniger-Follert, 1978]. Its relaxant effect on the smooth muscle of the vasculature is due to an inhibitory action on phosphodiesterase and mediated by accumulated cyclic-3′,5′-AMP [Kukovetz and Pöch, 1970].

According to unpublished data (S.E. Vizi) vinpocetine does not influence the quantity of ACh liberated from cholinergic neurons in rat cortical brain slices. Our experiments, which accord with those of DeNoble et al. [1986], show that vinpocetine has some direct or indirect facilitating effect on the acetylcholine system.

Vinpocetine exerted a beneficial effect in every test situation where memory and learning processes were impaired by scopolamine. Vinpocetine dose-dependently prevented the disrupting effect of scopolamine on the acquisition of a one-trial step-through passive avoidance task. In the prevention and restitution of scopolamine-induced retrograde amnesia, vinpocetine showed maximal effect, prevented, or restored the memory loss in the dose range tested. It has less, but still a significant, influence on retrieval of memory when the consolidation process has been disturbed by scopolamine. In the latter three tests the dose–effect curve of vinpocetine showed an inverted U-shape, with a maximal effect at 21.0 mg/kg (prevention of retrograde amnesia), 7.0 mg/kg (restitution of retrograde amnesia, retrieval), depending upon the test situation.

Among the reference compounds only vincamine showed a significant effect in two of the four tests (reversal of amnesia and recall of memory). Nicergoline, though it is a well-known antihypoxic agent [Truchaud and Moriniere, 1980; Truchaud, 1983; Shintomi et al., 1986] and increases learning ability in animals [Paul et al., 1978; Paul and Chandra, 1979], had no considerable activity in the tested situation. Papaverine was completely without effect.

The effectivity of vinpocetine in scopolamine-induced amnesic situations may be connected with its beneficial effect in ECS- and hypoxia-induced amnesic states, and may explain its therapeutic activity in human mental and cognitive impairments following transitory or permanent hypoxic states of circulatory or metabolic origin (Hadjiev and Iancheva, 1976; Szobor and Klein, 1976; Otomo et al., 1985; Tamaki et al., 1985]. At the same time there is a possibility that vinpocetine will have a favorable effect in Alzheimer disease as well.

The biochemical verification of the direct or other neurotransmitter-mediated effect of vinpocetine on the ACh system will elucidate better its mechanism of action, and explain further the functional relationship between hypoxic states following cerebral vascular incidents or senile ischemic cerebrovascular disease, cholinergic malfunctioning, and loss of memory.

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