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General Neuropharmacology of Vinpocetine: A Putative Cerebral Activator

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ABSTRACT

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Results from a series of standardized tests in rodents were used to describe the general neuropharmacology of vinpocetine, a putative cerebral activator. Vinpocetine was tested at doses ranging from 5 to 100 mg/kg p.o.; these doses are greater than its behaviorally active doses (i.e., 1 to 5 mg/kg p.o.). Vinpocetine did not impair rotarod performance or produce ataxia in mice. Vinpocetine antagonized electroconvulsive shock (ECS)-induced convulsions in rats (ED_{50} = 28 mg/kg p.o.); however, neither ECS- nor pentylenetetrazol (PTZ)-induced convulsions in mice were prevented by vinpocetine. The compound did not attenuate aggressive behavior in isolated mice. Vinpocetine decreased spontaneous locomotor activity (SLA) without affecting the rectal temperature in rats at doses greater than 25 mg/kg p.o., but the decrease was not dose-related. Neither 10 nor 50 mg/kg p.o. of vinpocetine antagonized amphetamine-induced stereotypy and exophthalmos in rats. In mice, vinpocetine (up to 100 mg/kg p.o.) did not antagonize reserpine-induced catalepsy and ptosis or protect against tremorine-induced lacrimation, tremor, salivation, or hypothermia. The lack of effect in these tests demonstrates that vinpocetine has little, if any, propensity to produce central nervous system (CNS) side effects.

Key words: vinpocetine, neuropharmacology, cerebral activator, cognition, central nervous system (CNS), rodents

INTRODUCTION

Vinpocetine (3α,16α eburnamenine 14-carboxylic acid ethyl ester; Fig. 1) is reported to prevent memory impairment in mice [Kiss et al., 1982; Groo et al., 1987]. It has also been shown that vinpocetine causes desynchronization of the electrocorticogram (ECoG) in rats

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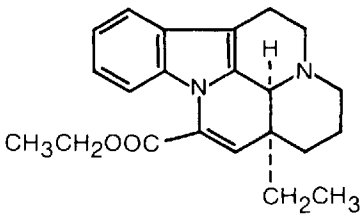

Fig. 1. The chemical structure of vinpocetine (3α, 16α eburnamenine 14-carboxylic acid ethyl ester).

[Notvest et al., 1986], indicating a vigilance-promoting effect. Additionally, in the cerebral-ischemic rat vinpocetine reportedly delayed the onset of seizures [King et al., 1985]. Of clinical relevance is that vinpocetine significantly improved short-term memory of volunteers [Subhan and Hindmarch, 1985].

Cerebrovasodilation was originally proposed as the mechanism for the behavioral effects described for vinpocetine. These data have been reviewed elsewhere [Fekete et al., 1976]. Most of the work that lead to this conclusion was performed in anesthetized animals and in most cases following intravenous administration. More recent work suggests, however, that cerebral perfusion does not increase in conscious vinpocetine-treated rats [Ferrone et al., 1986], at least not following oral administration of vinpocetine within the dose range (i.e., 1 to 10 mg/kg p.o.) and time schedule in which the ECoG changes have been recorded [Notvest et al., 1986].

Regarding the preclinical neuropharmacologic effects of vinpocetine, the only data available is from animals given vinpocetine intraperitoneally [Palos and Szporny, 1976]. The purpose of the present report is to document the profile of vinpocetine in standard neuropharmacologic tests following oral administration. A preliminary account of some of these results has been presented [Keim et al., 1986].

MATERIALS AND METHODS

Animals

Male Swiss albino mice or male Sprague-Dawley rats were used (Charles River Breeding Laboratories, Wilmington, MA). They were housed in environmentally controlled quarters with free access to food and water until the beginning of the experiment. The animals were acclimated to the vivarium for at least one week prior to use.

Test Procedures: Ataxia in Mice

A rotarod apparatus (25mm diameter, 6 rpm) was used to assess ataxia in mice. The animals (n = 6 per group, 18 to 22 g) were administered vinpocetine orally at 10, 30, or 100 mg/kg. Thirty min later ataxia was evaluated in the course of a 1-min test,* at 30-min intervals for at least 2 h after oral administration, and mice were considered ataxic if they fell more than once from the rotarod.

Anticonvulsant Activity

Mice (n = 8 per group, 20 to 24 gm) were dosed orally 1 h before being subjected to electroconvulsive shock (ECS). A constant current, square-wave direct current (DC) stimulus (Ugo Basile, ECT No. 7801; 200 Hz, 1 msec duration, 30 mA intensity for 0.3 sec) and corneal electrodes were used. Rats (n = 6 per group, 180–200 g) were also given ECS 1 h after oral administration of vinpocetine. In this case the electroshock was a 60 Hz AC sine wave of 35 mA for 0.25 sec (ECS Hans Technical Apparatus 2C) and was applied through two electrodes placed bilaterally against the temporal region of the rat's head between the eyes and the pinnae. ECS caused tonic convulsions in all vehicle-treated animals. The results were

expressed as the percentage of animals protected from the tonic extensor component of the seizure. Graded doses of vinpocetine were tested, and the results were summarized by the ED_{50} value.

Inhibition of Pentylenetetrazol-Induced Convulsions in Mice

Mice (n = 6 per group, 20 to 24 g) were dosed orally, and 60 min later pentylenetetrazol (PTZ; 125 mg/kg s.c.) was administered to all animals. In vehicle-treated mice, PTZ produced clonic convulsions that progressed to tonic extensions of the body within 15 min.

Attenuation of Isolation-Induced Fighting in Mice

Mice (14–16 g) were isolated for six weeks according to a published method [Valzelli et al., 1967]. This isolation induced an aggressive behavior, manifested by fighting whenever two isolated mice were placed in the same cage. Only those mice that exhibited fighting were used to evaluate the effects of vinpocetine. The animals were observed during a control session in the morning to ascertain whether fighting occurred in both members of the pair. Three groups of five pairs each were given vinpocetine orally and tested again for fighting 1 and 3 h later. An effect of the test compound was evaluated on an all-or-none basis; i.e., the compound was considered effective if no episodes of fighting occurred during the 5-min observation period.

Spontaneous Locomotor Activity (SLA) and Rectal Temperature in Rats

The apparatus is similar to the one used by Ljungberg and Ungerstedt [1978]. It consists of a square open field (69 × 69 cm with 25cm high walls, made of black plastic) around the periphery of which an animal can move freely. The middle of the open field is inaccessible because of a centrally placed cube (26 × 26 cm) of the same height as the walls. The apparatus was located in a darkened, quiet room illuminated by a 100-watt red light. The movements of the animals were detected by interruptions of ten photobeams that symmetrically covered the open-field area. Total activity was defined as the number of interruptions of the ten photobeams. The activity data were totaled and recorded at 10-min intervals. The rats (n = 6–8 per group, 240–260 g) were dosed orally 30 min prior to being placed individually into the apparatus. During this 30-min period the rats were kept in the darkened, quiet room for acclimatization. Just prior to the administration of vinpocetine, the rectal temperature of each rat was recorded. Rectal temperature was taken again 1 h after injection (i.e., after 30 min of acclimatization plus 30 min of locomotor testing). The mean total activity (± SEM) of the vinpocetine-treated rats was expressed as the percentage change relative to the vehicle-treated control.

Prevention of Reserpine-Induced Ptosis

Mice (n = 6 per group, 20–24 g) were treated orally with vinpocetine, and 60 min later reserpine (3 mg/kg s.c.) was administered to all animals. Ninety min after reserpine, ptosis was scored as follows: 4, complete eyelid closure; 3, 3/4 closure; 2, 1/2 closure; 1, 1/4 closure of the eyelids; and 0, normal opening of the eyes. The mean ptotic scores were calculated, and the results were expressed as the percent protection relative to the vehicle-treated animals.

Antagonism of Reserpine-Induced Catalepsy

Seventeen h after the administration of reserpine at a dose of 5 mg/kg i.p., a mouse was placed on a rubber stopper measuring 5 cm in diameter and 2.5 cm in height. The mouse was observed for three minutes. Mice that remained on the stoppers during this period were considered cataleptic, and six of these cataleptic mice were subsequently administered vinpocetine orally. The mice were retested on the stopper for vinpocetine's ability to antagonize reserpine's effect 0.5, 1, and 2 h later.

Antagonism of Tremorine-Induced Effects in Mice

Groups of six mice were used, and the experimental room temperature was monitored and maintained at 22 ± 1 °C. The rectal temperature of each mouse was measured at the beginning of the experiment. Vinpocetine was administered orally at doses of 10, 30, or 100 mg/kg, and 1 h later 20 mg/kg i.p. tremorine was injected. Hypothermia, tremor, salivation, and lacrimation were assessed 30 min after the tremorine injection. The rectal temperature of each mouse was again taken, and the mean temperature difference was determined for each group. Tremor was assessed visually and scored as follows: 2, pronounced, constant tremor; 1, moderate or intermittent tremor; 0, no tremor. The mean of the individual scores or the "tremor index" was determined for each group of mice. Salivation and lacrimation were assessed by a descriptive, all-or-none criterion.

Effect on d-Amphetamine-Induced Stereotyped Behavior

Rats (n = 4 per group, 160–180 g) were given vinpocetine at doses of 10 or 50 mg/kg or the vehicle orally. Sixty min later, the animals were given d-amphetamine at a dose of 5 mg/kg i.p. to test for the possible effect of vinpocetine on the stereotypy induced by d-amphetamine. Behavioral observations were made at 15-min intervals for the first 4 h and at 30-min intervals thereafter until termination of the experiment. At each h, the rats were also examined for the presence or absence of exophthalmos, which was assessed on an all-or-none basis. Stereotypy was scored according to the following scale [Voith and Herr, 1975]: 2, stereotypic (rats kept their nose on the grid of the cage floor and continuously licked or bit the wires; they remained in one spot or moved backwards over a small area); 1, excited (rats sniffed the grid of the cage, mostly at the walls and ceiling, and only transiently at the floor; they moved around the cage usually keeping their heads elevated); 0, normal (rats divided their time between occasional exploration, sniffing, grooming, and sleeping).

Compounds

Vinpocetine (Ayerst Laboratories, NY) was prepared daily, suspended in 0.5% w/v methyl cellulose for oral administration. Methyl cellulose served as the vehicle, and vehicle-treated animals were tested accordingly. The concentrations of the solutions were such that mice received a volume of 10 ml/kg and rats received 4 ml/kg body weight. The following compounds were also used: reserpine injectable USP (Serpasil, CIBA), d-amphetamine sulfate (Sigma), oxotremorine sesquifumarate (Aldrich), and PTZ (Sigma); these chemicals were dissolved in distilled water. The dosages are expressed in terms of the base substance.

Statistics

Depending upon the screening test and/or the experimental design, the data were analyzed by analysis of variance (ANOVA), Dunnett's t test, or the Chi Square test for significance. An alpha value of less than 0.05 was considered statistically significant. The mean difference of the pretreatment and post-treatment rectal temperatures was analyzed by the paired t test. The ED_{50} values were calculated according to the method of Litchfield and Wilcoxon [1949].

RESULTS

Ataxia

None of the mice treated with vinpocetine at doses of 10, 30, or 100 mg/kg p.o. fell from the rotarod. Signs of hyperactivity, exophthalmos, stereotypic sniffing, and climbing behavior were seen in some of the mice treated with 30 or 100 mg/kg of vinpocetine.

Anticonvulsant Activity

Neither 10, 30, nor 100 mg/kg p.o. of vinpocetine protected mice from tonic convulsions induced by ECS. In contrast, vinpocetine antagonized the ECS-induced tonus in rats following

oral administration with an ED_{50} value of 28 mg/kg p.o. The 100 mg/kg dose of vinpocetine protected all of the treated rats from tonic convulsions.

Vinpocetine at doses of 10, 30, or 100 mg/kg p.o. did not protect mice from PTZ-induced convulsions. There was a nonsignificant trend for the latency to tonic seizures to be prolonged in the vinpocetine-treated groups (mean, 9.8 min) when compared with the vehicle-treated control group (mean, 7.5 min).

Isolation-Induced Behavior in Mice

Isolation-induced fighting behavior in mice was not attenuated by vinpocetine at doses up to 100 mg/kg p.o.

Spontaneous Locomotor Activity (SLA) and Rectal Temperature in Rats

The effect of vinpocetine upon SLA of rats is illustrated in Figure 2. After an oral dose of 5 mg/kg vinpocetine, total activity did not significantly differ from that of vehicle-treated rats during the 30-min test period. A significant ($P < 0.01$) decrease in SLA was recorded in rats treated with 25 (−45%), 50 (−52%), and 100 (−47%) mg/kg p.o. of vinpocetine, but the decrease was not dose-related.

At the doses tested, vinpocetine did not produce any significant change in the rectal temperature of rats. The difference between the pretreatment and post-treatment rectal temperature was less than 1°C.

Reserpine-Induced Effects

Vinpocetine at doses up to 100 mg/kg p.o. did not antagonize reserpine-induced catalepsy or reserpine-induced ptosis in mice. The 17% protection in catalepsy and 13% decrease in mean ptotic score in mice treated with 100 mg/kg p.o. vinpocetine were not significant.

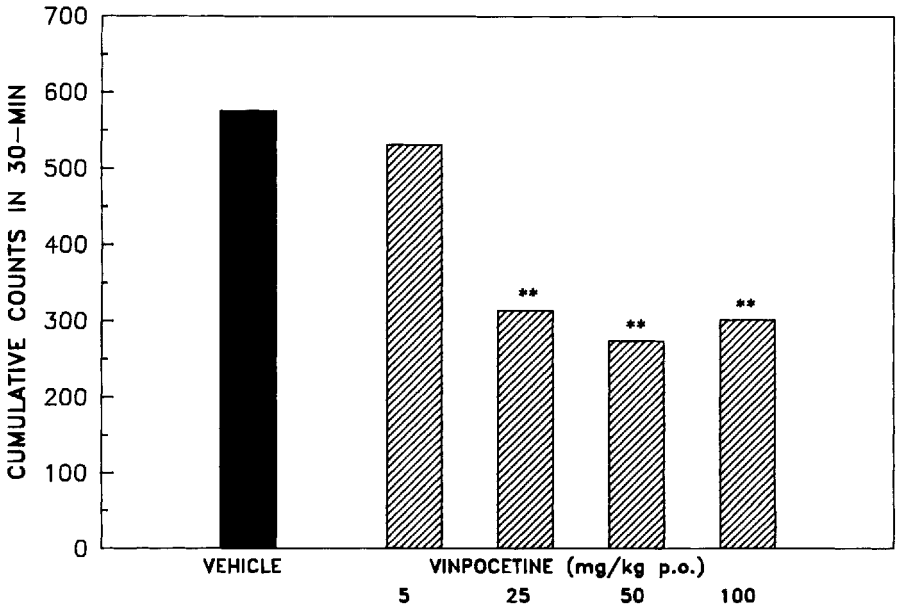

Fig. 2. The effect of vinpocetine on locomotor activity in rats. Rats (n = 6 to 8 per group) were tested individually in a Ljungberg and Ungerstedt open-field apparatus in which spontaneous activity was quantified in a darkened room by the interruption of photobeams. Cumulative counts for a 30-min test period began 30 min following oral administration of vinpocetine (** $P < 0.01$).

Antagonism of Tremorine-Induced Effects in Mice

At doses up to 100 mg/kg p.o. vinpocetine did not antagonize either the central nervous system (CNS) effects (i.e., tremor and hypothermia) or the peripheral effects (i.e., salivation and lacrimation) of tremorine.

Effect on d-Amphetamine-Induced Stereotypic Behavior

Neither 10 nor 50 mg/kg p.o. of vinpocetine attenuated amphetamine-induced stereotypic behavior; however, the mean stereotypic score elicited by 5 mg/kg i.p. of amphetamine was increased by both doses (Fig. 3). Amphetamine-induced exophthalmos was not effected by vinpocetine.

DISCUSSION

This paper summarizes the general neuropharmacology of vinpocetine, a cerebral activator, evaluated in a series of standardized tests in rodents. Measurements were made 30 to 90 min following oral administration, a pretreatment time that coincides with the peak blood level of vinpocetine in rats [Vereczkey et al., 1979]. The neuropharmacologic profile of vinpocetine can be described as "unremarkable" and is summarized in Table 1. An important assessment of the compound's acute safety profile is its lack of effect in classic tests for CNS activity while maintaining activity in tests of learning and memory. Vinpocetine's oral LD_{50} value in mice and rats is in excess of 1,000 mg/kg (unpublished data), and, taken together, these preclinical data suggest that vinpocetine is a safe compound with low propensity to produce unwanted side effects.

Vinpocetine at oral doses of 100 mg/kg in mice did not impair the evoked motor response of negotiating a rotating rod. It is well-known that most psychotropic agents, other than the "nootropics," affect motor coordination. Lower doses of vinpocetine, specifically 25 and 50 mg/kg p.o., reduced emitted behavior in rats as measured by quantifying SLA. Others

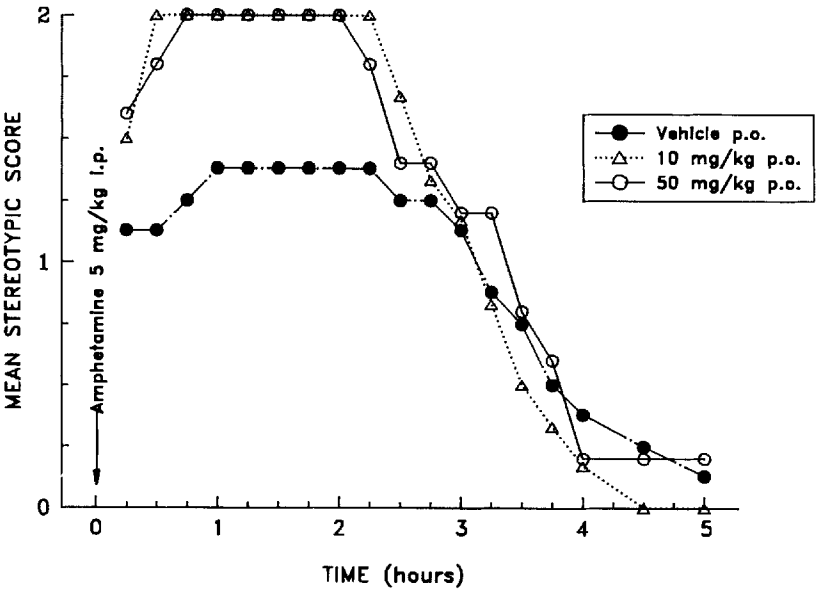

Fig. 3. The effect of vinpocetine on amphetamine-induced stereotyped behavior in rats. One hour after vinpocetine, rats (n = 4 per group) were given 5 mg/kg i.p. d-amphetamine, and behavioral observations were made at 15-min intervals. Stereotypy was scored as: 2, stereotypic; 1, excited; 0, normal behavior. See text for more details.

TABLE 1. Summary of Neuropharmacological Effects of Orally Administered Vinpocetine

Species/test	Doses tested (mg/kg p.o.)	Significant effect
Mice		
Ataxia	10, 30, 100	None
Anti-ECS	10, 30, 100	None
Anti-PTZ	10, 30, 100	None
Anti-aggressive	30, 100	None
Anti-reserpine ptosis	10, 30, 100	None
Anti-reserpine catalepsy	10, 30, 100	None
Anti-tremorine effects	10, 30, 100	
Lacrimation		None
Hypothermia		None
Salivation		None
Rats		
Anti-ECS	5, 25, 50, 100	$ED_{50} = 28$
Spontaneous locomotor activity	5, 25*, 50*, 100*	* = decrease
Rectal temperature	5, 25, 50, 100	None
Anti-amphetamine[a]	10, 50	
Stereotypic intensity		Enhanced
Duration of stereotypy		No change
Exophthalmos		None

*5 mg/kg i.p.

have reported a decrease in SLA in mice following intraperitoneal administration of vinpocetine [Palos and Szporny, 1976]. However, the doses that decreased SLA in our studies are still well above the 3 and 10 mg/kg dose of vinpocetine that protected rats from hypoxia-induced impairment of the passive avoidance response [unpublished data]. Moreover, neither decreased muscle tone nor sedative effects were evident in rats treated with vinpocetine. Although different species were tested, we concluded that since vinpocetine did not impair rotarod performance or decrease SLA at behaviorally active doses, it has a relatively low potential to cause sedative effects in young mature rodents.

The weak anticonvulsant activity of vinpocetine is a characteristic it shares with other cerebral activators/nootropics. Because tonic seizures induced by PTZ in mice were not antagonized, it is concluded that vinpocetine is not benzodiazepine-like in its anticonvulsant activity but more phenytoin-like. These findings corroborate an earlier report [Palos and Szporny, 1976] of vinpocetine's action when given parenterally. Piracetam and the "acetam" analogs are similarly anticonvulsant at higher doses [Cumin et al., 1982]; however, it is not known whether the weak anticonvulsant activity demonstrated in preclinical tests has clinical relevance. In this regard, Ezzat and coworkers recommend premedication of patients undergoing electroconvulsive therapy with piracetam to reduce memory loss [Ezzat et al., 1985], and at least one clinical investigator has indicated limited success with low doses of the anticonvulsant agent phenytoin in some demented patients [B. Reisberg, personal communication].

The fact that, in mice, vinpocetine did not reduce the fighting behavior induced by isolation supports a previous observation [Palos and Szporny, 1976]. Compounds found active in this test have been classified as antiaggressive or anxiolytic agents; antipsychotics also produce a taming effect. Clearly, vinpocetine does not share these pharmacologic characteristics with classical psychotropic agents.

Vinpocetine did not prevent the ptosis or catalepsy produced by reserpine. Thus, the test compound cannot be claimed to have an antidepressant activity as defined by these classic screening tests. However, Schmidt [1984] recently found vinpocetine to decrease the immobility in mice associated with the "behavioral despair" test described by Porsolt. Because vinpocetine did not antagonize tremorine-induced effects and amphetamine-induced exophthal-

mos, it can also be stated that, except at the higher dose, it is devoid of peripheral or central anticholinergic and peripheral antiadrenergic actions.

It is interesting that vinpocetine enhanced the intensity of stereotypy in rats treated with 5 mg/kg of amphetamine. Unless the metabolism of amphetamine was affected in vinpocetine-treated animals, vinpocetine must somehow be altering changes induced by amphetamine in aminergic neurotransmission. Amphetamine is a pharmacological activator; low doses release norepinephrine and dopamine throughout the brain resulting in enhanced coordinated locomotor activity [Lyon and Robbins, 1975]. It is reasonable to assume that higher doses of amphetamine released dopamine in the striatum; dopamine is the neuropharmacologic trigger for stereotyped responding. Brain dopamine systems are crucial in unconditioned and conditioned learning, memory consolidation, and cognitive function [Iversen, 1977], as are the central noradrenergic pathways critical for attention, learning, and memory [Amaral and Foss, 1975; Koob et al., 1978; Mason and Iversen, 1978]. Vinpocetine reportedly causes selective increase in the turnover of brain norepinephrine without a significant change in the turnover of dopamine or serotonin (Kiss et al., 1982), although a nonselective increase in the turnover of the three amines has been reported (Chang, 1985). These aminergic pathways may be partially mediating the effects of vinpocetine. Vinpocetine is active in the Porsolt-test of swim immobility, albeit at higher doses [Schmidt, 1984]. It is reported that vinpocetine has central phosphodiesterase inhibitory activity [Rosdy et al., 1976] and is claimed to increase brain glucose uptake [Shibota et al., 1982], and these effects may also contribute to its actions on the CNS.

In conclusion, a series of tests were performed to describe the neuropharmacology of vinpocetine, an agent with cerebral activating properties. The results indicate that at doses which enhance learning and memory and activate the electrocorticogram in rats (i.e., 1 to 10 mg/kg p.o.), vinpocetine does not impair motor function or alter body temperature and is devoid of significant anticonvulsant, antiaggressive, anticholinergic, or adrenergic activity. Thus, vinpocetine has a low propensity for producing behavioral side effects.

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REFERENCES

Amaral, D.G., and Foss, J.A.: Locus coeruleus lesions and learning. Science **188:**377–378, 1975.

Chang, K.-H.: A pharmacological study on drugs acting on the cerebral circulatory dynamics—effects of vinpocetine on brain monoamines in rats, a vincamine derivative. Tokyo Ika Kaigaku Zasshi **43:**207–220, 1985.

Cumin, R., Bandle, E.F., Gamzu, E., and Haefely, W.E.: Effects of the novel compound aniracetam (RO 13-5057) upon impaired learning and memory in rodents. Psychopharmacology **78:**104–111, 1982.

Ezzat, D.H., Ibrahum, M.M., and Makhawy, B.: The effect of piracetam on ECT-induced memory disturbances. Br. J. Psychiatry **147:**720–721, 1985.

Fekete, G.Y. et al. In Arzneim-Forsch (Drug Res.-Series) 1976; **26:**1905–1989.

Ferrone, R.A., Ward, D., Urbancic, A., and Keim, K.L.: Acute and subchronic effects of vinpocetine on systemic and regional hemodynamics in conscious rats. Soc. Neurosci. Abstr. **12:**704, 1986.

Groo, D.E., Palosi, E., and Szporny, L.: Effects of vinpocetine in scopolamine-induced learning and memory impairments. Drug Dev. Res. **11:**29–36, 1987.

Iversen, S.D.: Brain dopamine systems and behavior. In "Handbook of Psychopharmacology, " Vol. 8, New York: Plenum Press, 1977, pp 333–385.

Keim, K.L., Hall, P.C., King, G.A., Shieh, I.S., and Lee, D.: Neuropharmacology of vinpocetine, a putative cerebral activator. Soc. Neurosci. Abstr. **12:**703, 1986.

King, G.A., Narcavage, D., Romanski, L., Hannig, D., and Shieh, A.: Effects of vinpocetine in a rat model of cerebral ischemia. Soc. Neurosci. Abstr. **11**:433, 1985.

Kiss, B., Lapis, E., Palosi, E., Groo, D., and Szporny, L.: Biochemical and pharmacological observations with vinpocetine, a cerebral oxygenator. In Wauguier A, Borgers M, Amery WK (eds.): "Protection of Tissues Against Hypoxia," Vol. 7. International Symposium on Protection of Tissues Against Hypoxia, Beerse, Belgium, September 15–17, 1982. Amsterdam, Holland: Elsevier Biomedical Press, 1982, pp. 305–309.

Koob, G.F., Keeley, A.E., and Mason, S.T.: Locus coeruleus lesions: learning and extinction. Physiology and Behavior **20**:709–716, 1978.

Litchfield, J.T., and Wilcoxon, P.: A simplified method of evaluating dose-effect experiments. J. Pharmacol. Exp. Ther. **96**:99–113, 1949.

Ljungberg, T., and Ungerstedt, U.: A method for simultaneous recording of eight behavioral parameters related to monoamine neurotransmission. Pharmac. Biochem. Behav. **8**:483–489, 1978.

Lyon, M., and Robbins, T.: The action of central nervous system stimulant drugs: a general theory concerning amphetamine effects. In "Current Developments in Psychopharmacology," Vol. 2, New York: Halsted Press, pp. 80–163.

Mason, S.T., and Iversen, S.D.: Reward, attention and the dorsal noradrenergic bundle. Brain Res. **150**:135–148, 1978.

Notvest, R.R., Inserra, J.J., and Emrey, T.: Effect of vinpocetine on the resting electrocorticogram (ECoG) of 3-month-old rats. Soc. Neurosci. Abstr. **12**:704, 1986.

Palos, E., and Szporny, L.: Effects of ethyl apovincaminate on the central nervous system. Arzneim-Forsch (Drug Res.) **26**:1926–1926, 1976.

Rosdy, B., Balazs, M., and Szporny, L.: Biochemical effects of ethyl apovincaminate. Arzneim-Forsch **26**:1923–1928, 1976.

Schmidt, J.: Nootropic drugs reduce immobility in behavioral despair test in mice. Biomed. Biochem. Acta **11**:1295–1299, 1984.

Shibota, M., Kakihana, M., and Nagaoka, A.: The effect of vinpocetine on brain glucose uptake in mice. Folia Pharmacol. Jpn **80**:221–224, 1982.

Subhan, Z., and Hindmarch, I.: Psychopharmacological effects of vinpocetine. Eur. J. Clin. Pharmacol. **28**:567–571, 1985.

Valzelli, L., Giacalone, E., and Garattini, S.: Pharmacological control of aggressive behavior in mice. Eur. J. Pharmacol. **2**:144–146, 1967.

Vereczkey, L., Szentirmay, Z.S., and Szporny, L.: Kinetic metabolism of vinpocetine in the rat. Arzneim-Forsch (Drug Res.) 29(I) **6**:953–956, 1979.

Voith, K., and Herr, F.: The behavioral pharmacology of butaclamol hydrochloride (AY-23,028), a new potent neuroleptic drug. Psychopharmacologia (Berl.) **42**:11–20, 1975.