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Effect of Vinpocetine on Monoamine Receptor Binding and Synaptosomal Uptake in the Rat Brain

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ABSTRACT

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The in vitro effect of vinpocetine on the various adrenergic, serotoninergic, and dopaminergic receptor systems was studied in the rat. At 1 μM concentrations, vinpocetine and its major metabolite, apovincaminic acid, did not exhibit inhibitory activity in any of the receptor binding assays, nor did vinpocetine show any significant inhibitory effect in the synaptosomal uptake assays at ten-fold higher concentrations. The results suggest the unlikeliness that vinpocetine exerts its pharmacological effects through monoamine receptor binding or synaptosomal uptake mechanisms.

Key words: monoamine, brain, rat, receptor, synaptosome

INTRODUCTION

Vinpocetine, an eburnamenine derivative, is reported to have a protective effect in cerebral ischemia, both in animals [Biro et al., 1976; King and Narcavage, 1986; King, 1987] and in man [Otomo et al., 1985; Tamaki et al., 1985]. Although its mechanism of action is still unknown, it has been shown, in vivo, to alter brain monoamine concentrations and accelerate the rate of norepinephrine turnover [Rosdy et al., 1976; Ishida et al., 1982]. The present communication is concerned with the in vitro effect of vinpocetine on receptor binding and synaptosomal uptake of monoamines in the rat brain. Apovincaminic acid (AVA), the major circulating metabolite of vinpocetine [Vereczkey and Szporny, 1976; Kuzuya, 1982], was also tested in the receptor binding assays.

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TABLE 1. Effect of Vinpocetine and AVA on Various Receptor Systems

Receptor system	Tissue	[^{3}H]ligand	% inhibition[a] Vinpocetine	% inhibition[a] Apovincaminic acid	IC_{50} (nM) of Reference compounds
α_1	Cortex	Prazosin	9[b]	0	1.0 for prazosin
α_2	Cortex	Rauwolscine	16	0	11.5 for rauwolscine
β_1	Cortex	Dihydroalprenolol	3	6	6.1 for (−)propranolol
β_2	Cerebellum	Dihydroalprenolol	0	0	4.9 for (−)propranolol
$5HT_1$	Hippocampus	Serotonin	0	0	35.7 for serotonin
$5HT_2$	Frontal cortex	Ketanserin	0	0	4.2 for methysergide
DA agonist	Corpus striatum	Apomorphine	5	0	9.8 for apomorphine
DA antagonist	Corpus striatum	Spiroperidol	0	0	5.7 for (+)butaclamol

[a]Compounds were tested at 1 μM except in the $5HT_1$ assay, where 10 μM concentrations were used.
[b]All values are the average of triplicate determinations.

MATERIALS AND METHODS

Male Sprague-Dawley rats from Charles River Breeding Labs (Wilmington, MA) were decapitated, and selected brain regions were quickly excised and prepared for the various binding and uptake assays. Vinpocetine and AVA were obtained from Gedeon Richter (Budapest, Hungary). All other chemicals and radiolabeled compounds were obtained from commercial sources.

The methods detailing the α_1-, α_2-, β_1-, β_2-adrenoceptor, and serotonin $(5HT)_1$ and $5HT_2$ receptor binding assays have been described elsewhere [Grimes et al., 1987]. The dopamine (DA) receptor agonist binding assay was performed by the methods of Hamblin and Creese [1982] and Sokoloff et al. [1980]. The DA receptor antagonist binding assay was carried out as described by Gundlach [1984]. Uptake studies were performed by the method of Glowinski and Iversen [1966]. Specific binding or uptake values obtained in the presence of test compound were calculated as a percentage of that in the absence of test compound. IC_{50} values (concentration of drug producing a 50% inhibition) were determined from a logit-log plot of concentration of test compound vs. percent inhibition of specific binding or uptake.

RESULTS AND DISCUSSION

The results of the receptor binding assays are shown in Table 1. At 1 μM, neither vinpocetine nor AVA exhibited any affinity for the receptors tested. In comparison, the reference compounds showed IC_{50} values in the nanomolar range; i.e., values that agree with those reported in the literature.

In the synaptosomal uptake studies, vinpocetine did not show significant inhibitory activity at 10 μM concentration, whereas the reference compounds inhibited their respective ligand uptakes at greater than 100-fold lower concentrations (Table 2).

In clinical trials, oral doses of 40 mg of vinpocetine for two days significantly improved the short-term memory of volunteers [Subhan and Hindmarch, 1985]. Global improvement in patients with sequelae of cerebral infarction, hemorrhage, arteriosclerosis, and transient ischemic attacks was observed after four weeks of treatment with 15 mg per day [Otomo et al., 1985]. An oral dose of 10 mg of vinpocetine gave rise to maximum plasma concentrations of 0.01 to 0.17 μM of vinpocetine [Vereczkey et al., 1979; Kuzuya, 1982]. Thus, it appears that at clinically effective doses vinpocetine is not likely to exert its activity via receptor-mediated changes in the monoamine systems tested in the present study. However, the possibility that vinpocetine may be selectively concentrated in the brain, or that other neural mechanisms such as turnover rates and the cholinergic system may be involved, cannot be ruled out.

TABLE 2. Effect of Vinpocetine on the Synaptosomal Uptake of Monoamines

Synaptosomal system	Tissue	[^{3}H]ligand	% inhibition at 10 μM of vinpocetine	IC_{50} (nM) of reference compounds
DA	Corpus striatum	DA	45[a]	170 for benztropine
Norepinephrine	Hypothalamus	Norepinephrine	0	4 for desipramine
5HT	Hypothalamus	5HT	12	5 for chlorimipramine

[a]Each value is the average of triplicate determinations.

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