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Effects of Isradipine and Darodipine on Serotonergic System of the Rat Brain

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GAGGI, R., R. DALL'OLIO, P. RONCADA AND A. M. GIANNI. *Effects of isradipine and darodipine on serotonergic system of the rat brain.* PHARMACOL BIOCHEM BEHAV **51**(2/3) 183–187, 1995.—Isradipine and darodipine are dihydropyridine calcium antagonists that easily pass into the brain, showing high affinity for cerebral L-type voltage-sensitive calcium channel (VSCC). These drugs were IP administrered to rats to study their effects on serotonergic systems of discrete brain areas. Isradipine (0.05–5.0 mg/kg) and darodipine (0.3–20 mg/kg) increased the 5-HIAA/5-HT ratio, mostly enhancing the metabolite (5-HIAA) content in various brain areas, suggesting that serotonin (5-HT) turnover was increased. This increase appeared to depend on facilitation of serotonergic neurotransmission, because low doses of isradipine (<0.075 mg/kg) or darodipine (<0.6 mg/kg) enhanced the number of head twitches induced by L-5-hydroxytryptophan (L-5-HTP). However, higher doses of isradipine (1.5 mg/kg) or darodipine (5 mg/kg) also appeared to stimulate a negative feedback mechanism, which predominated over the facilitation when the serotonergic neurotransmission was strongly activated. Thus, higher drug doses decreased both the serotonin turnover and the number of head twitches on rats treated with L-5-HTP. It was speculated that the observed effects were due to brain VSCC blockade, although the studied compounds showed a peculiar profile of properties when compared to other previously studied calcium antagonists. Moreover, it was concluded that darodipine appeared to be more effective and selective than isradipine regarding the effects on brain serotonergic systems.

Isradipine Darodipine Rat brain areas Serotonergic system Serotonin Serotonin precursor and metabolite Head twitches

STRONG evidence suggests that calcium antagonists display several effects on the CNS, directly acting on the L-type neuronal voltage-sensitive calcium channel (VSCC). On the basis of animal studies it was reported that these drugs possess antidepressant (8), neuroleptic (22), and anxiolytic-like (23) properties, as well as anticonvulsant (7) and analgesic activity (1). Moreover, calcium antagonists were found to inhibit abstinence syndrome in alcohol (23)- or morphine-addicted (4) animals. Some clinical trials (9,18,24) appear to corroborate the animal data.

The neurochemical mechanisms underlying the central effects induced by the calcium antagonists remain quite unknown, although some biochemical data, generally supporting both animal and clinical reports, suggest a prominent involvement of monoaminergic systems (5,10,13,24).

In particular, several compounds were found to increase the serotonin (5-HT) turnover in various brain areas, suggesting activation of serotonergic systems. In this regard, dihydropyridine compounds appeared to be more effective than the nondihydropyridine ones (10). Peripherally administered nifedipine, nimodipine, and nisoldipine, showing an individual profile of effects, dose-dependently induce modest but statistically significant increase in the 5-hydroxy-3-indoleacetic acid (5-HIAA) levels and/or in the 5-HIAA/5-HT ratio (10–13). However, these effects on brain serotonin turnover, as well as the above-mentioned effects, are induced at doses that display marked peripheral (i.e., vasodilatory and cardiodepressive) effects.

On the other hand, calcium antagonists could represent (9,24) a novel class of psychotropic drugs only when would be developed highly selective compounds that, besides crossing the blood–brain, bind to brain VSCC more easily than to peripheral VSCC.

Isradipine (16) and darodipine (17) are isomers belonging to the dihydropyridine class of the calcium channel antagonists, which are sequestered by brain although highly bound to plasma albumin, α_1 acid glycoprotein, and lipoproteins. In fact, it has been shown (28) that the fraction of these drugs bound to albumin or α_1 acid glycoproteine is partially transported across the blood–brain barrier and that the entire frac-

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tion of the two drugs bound to lipoproteins is available for entry into the brain. Moreover, both isradipine and darodipine show higher affinity for VSCC than verapamil and other calcium antagonists (16,17,26) as well as higher affinity for the cerebral binding sites than for the heart binding sites (19,26).

The aim of the present paper was to study the action of peripherally administered isradipine and darodipine on the serotonergic system. To this purpose, the effects of the drugs either on the serotonin turnover in discrete rat brain areas or on L-5-hydroxytryptophan (L-5-HTP)-induced head twitches were evaluated.

Finally, the interactions of isradipine and darodipine with a drug that activates the serotonergic systems (i.e., the immediate metabolic precursor of serotonin L-5-HTP) were studied to elucidate the mechanisms of the effects induced by the two calcium antagonists on the serotonergic neurotrasmission.

METHOD

Animals

Male Sprague-Dawley rats (Charles River Italia S.p.A., Como, Italy) weighing 180–220 g were used. They were housed under standard laboratory conditions at 22°C with a 12L : 12D cycle (0700–1900 h) and free access to water and food. On the day of the experiment, the rats used in the biochemical studies were food deprived at 0900 h.

Experimental protocols were approved by a local Bioethical Committee and the procedures and animal comfort were controlled by the University Veterinary Service.

Drugs and Treatments

Isradipine and darodipine (Sandoz, Prodotti Farmaceutici S.p.A., Milano, Italy) were kindly supplied as powders, which were suspended with 1% Tween 80 in saline. The dose per kg was contained in 4 ml of suspension that was IP administered. The time between darodipine administration and animal killing was shorter than that of isradipine, because the effects of the latter drug had been found much longer lasting than those of darodipine (2). α-Methyl-DOPA-hydrazine (carbidopa, kindly supplied by Merck Sharp & Dohme, West Point, PA) was suspended with arabic gum 5% in saline and IP administered in a volume of 5 ml/kg. L-5-HTP (Sigma Inc., St. Louis, MO) was dissolved in saline acidified with HCl and SC injected in a volume of 4 ml/kg.

First Experiment: Effects of isradipine or darodipine on 5-HT and 5-HIAA content in brain areas of normal rats. On the basis of preliminary data, isradipine (0.05, 0.5, or 5 mg/kg) was administered 120–150 min before killing to groups of six rats. Darodipine (0.3, 1.5, 5, or 20 mg/kg) was injected 90 min before killing to groups of five rats. Control animals were treated with vehicle.

Second Experiment: Effects of isradipine or darodipine on L-5-HTP-induced head twitches. The rats (n = 6–12 per group) were treated with isradipine (0.019, 0.038, 0.075, 0.15, 0.3, 1.25, 5, or 20 mg/kg), darodipine (0.075, 0.15, 0.3, 0.6, 1.25, or 20 mg/kg), or vehicle. Thirty minutes after isradipine or immediately following darodipine injections, the animals received the peripheral decarboxylase inhibitor carbidopa (25 mg/kg); 30 min later they were administered L-5-HTP (100 mg/kg) and placed into transparent Plexiglas cylinders (20 cm diameter, 25 cm height) having the bottom covered with a thin layer of sawdust. Fifteen minutes later, experienced observers, unaware of the treatments, counted the number of head twitches exhibited by the animals in 90 min.

Third Experiment: Effects of isradipine or darodipine on 5-HTP, 5-HT, and 5-HIAA content in brain areas of L-5-HTP-treated rats. Groups of six rats were treated with isradipine at doses of 0 (vehicle), 0.05, or 1.5 mg/kg, or darodipine at doses of 0 (vehicle), 0.3, or 5 mg/kg. Forty minutes after isradipine or immediately after darodipine, the animals were given 25 mg/kg of carbidopa. Thirty minutes later they were treated with 20 mg/kg L-5-HTP. All rats were decapitated 60 min after L-5-HTP administration (i.e., 130 min after isradipine or 90 min after darodipine treatment).

Analytical Procedure

All the rats were decapitated in the afternoon (1600–1800 h) to avoid circadian variations in the brain serotonin and metabolite content. The brain was rapidly removed and immediately ice cooled. Olfactory tubercles and cerebellum were discarded, whereas hypothalamus, hippocampus, brain stem (pons + medulla oblongata), striatum, fronto-parietal cortex, and part of remaining tissue (mostly consisting of thalamus-midbrain) were dissected and rapidly frozen with pulverized dry ice. The samples were kept at −80°C until the time of analysis, which was performed within 10 days after collection. For each experiment, the same brain region was analyzed on the same day.

5-HTP, 5-HT, and 5-HIAA were determined simultaneously by high performance liquid chromatography with electrochemical detection following the method of Seegal et al. (25) modified as previously described (14) in detail. The method permits quantification of 50–100 pg of 5-HTP, 5-HT, and 5-HIAA. Isoproterenol was used as an internal standard.

Statistical Analysis

One-way ANOVA was applied to the biochemical data followed by two-tailed Dunnett's t-test to compare individual groups to the control. Linear correlation ratios between an effect and the log of the drug doses were computed as needed in the first experiment. Orthogonal comparison between the lower and the higher dose was also performed in the third experiment.

Behavioral data (number of head twitches exhibited by the animals in the 90-min observation period) were analyzed by Mann–Whitney U-test.

RESULTS

First Experiment: Effects of Isradipine or Darodipine on the 5-HT and 5-HIAA Content in Brain Areas of Normal Rats

All the treatments were well tolerated by the animals and did not induce changes in gross behavior except a little reduction of spontaneous motility when isradipine or darodipine was administered at doses of 5 mg/kg or more (data not shown).

In general, the studied drugs appeared to increase the 5-HT turnover in various brain areas. The effects on the 5-HIAA/5-HT ratio in the hippocampus and striatum are reported in Fig. 1 whereas the effects in the other brain areas are not shown. In particular, both isradipine and darodipine did not significantly change the 5-HT content of all brain areas. Isradipine increased the 5-HIAA levels (data not shown) of the

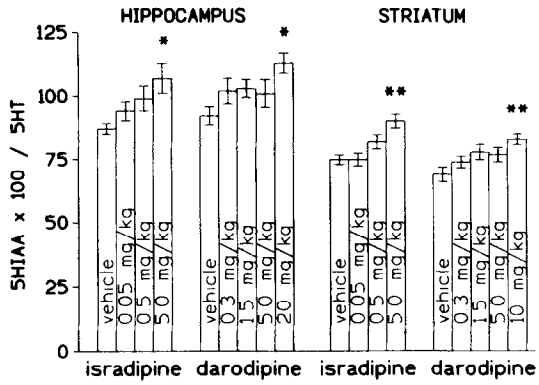

FIG. 1. Ratio between the 5-HIAA and 5-HT levels in the hippocampus and striatum of rats treated with different doses of isradipine or darodipine. The bars represent mean values ± SEM from groups of five (darodipine) or six (isradipine) animals. $*p < 0.05$; $**p < 0.01$ significantly different from the respective control (two-tailed Dunnett's t-test).

hippocampus, $F(3, 20) = 7.19$, $p < 0.01$, but this effect was not linearly correlated to the log-dose of the drug. The 5-HIAA/5-HT ratio was significantly increased by isradipine in the hypothalamus, $F(3, 20) = 4.09$, $p < 0.05$, hippocampus, $F(3, 20) = 3.46$, $p < 0.05$, and striatum, $F(3, 20) = 7.63$, $p < 0.01$, whereas darodipine did so in brain stem, $F(4, 20) = 2.88$, $p < 0.05$, hippocampus, $F(4, 20) = 2.86$, $p < 0.05$, striatum, $F(4, 20) = 3.63$, $p < 0.05$, and fronto-parietal cortex, $F(4, 20) = 3.16$, $p < 0.05$. However, the linear correlation log-dose effect was not statistically significant, except for data from striatum where both isradipine, $r(17) = 0.708$, $p < 0.01$, and darodipine, $r(19) = 0.880$, $p < 0.01$, dose-dependently affected the 5-HIAA/5-HT ratio.

Second Experiment: Effects of Isradipine or Darodipine on L-*5-HTP Induced Head Twitches*

Some preliminary experiments showed that both isradipine and darodipine, as well as nimodipine and other calcium antagonists, did not induce head twitches per se.

Figure 2 depicts the head twitch response induced by L-5-HTP (100 mg/kg, SC) in rats pretreated with different doses of isradipine or darodipine. Both drugs showed a similar behavioral pattern: the lower doses increasing and the higher doses reducing the response to the serotonergic stimulation. Nevertheless, isradipine was about 10 times more potent than darodipine.

Third Experiment: Effects of Isradipine or Darodipine on the 5-HTP, 5-HT, and 5-HIAA Content in Discrete Brain Areas of Rats Treated With L-*5-HTP*

The administration of L-5-HTP after inhibition of peripheral decarboxylase with carbidopa greatly increased the brain content of 5-HTP, 5-HT, and 5-HIAA. Thus, 20 mg/kg of L-5-HTP (instead of the dose used in behavioral assay) was administered to rats in this experiment. Similar changes in the content of serotonin precursor, amine, and metabolite were induced by isradipine or darodipine in all brain areas, with the effects of darodipine more marked than those of isradipine. The data regarding brain stem, hippocampus, and striatum are reported in Table 1, whereas the data obtained from hypothalamus, fronto-parietal cortex, and thalamus-midbrain are not shown. In general, the lower dose of isradipine or darodipine decreased the 5-HTP tissue levels as well as the 5-HTP/5-HT ratio, and increased the 5-HIAA content and the 5-HIAA/5-HT ratio. On the contrary, the higher dose of the drugs increased the 5-HTP content and the 5-HTP/5-HT ratio and decreased the 5-HIAA levels as well as the 5-HIAA/5-HT ratio. These data suggested that both isradipine and darodipine facilitated at the lower dose, but inhibited at the higher dose, the serotonergic neurotransmission activated by administration of L-5-HTP.

DISCUSSION

Intraperitoneal administrations of isradipine and darodipine to rats increased the brain 5-HIAA/5-HT ratio mostly by enhancing the 5-HIAA content of various cerebral areas. This agrees with previous findings regarding other dihydropyridine and nondihydropyridine calcium antagonists (10–13), suggesting that blockade of neuronal VSCC activate 5-HT turnover through unknown mechanisms.

However, isradipine and darodipine, unlike other calcium antagonists, induced effects that did not appear linearly correlated with the administered dose, except in the striatum. Therefore, it could be argued that an activation of 5-HT turnover displayed by the lowest doses of isradipine or darodipine was partially overcome by an inhibitory effect induced by the highest doses on the same process. The second experiment was performed to determine whether the enhancement of 5-HT turnover depended on the increase in the serotonergic neurotransmission, but also to verify differences between the effects of low or high drug doses on activated serotonergic systems. In fact, it has been reported that the effects of calcium antagonists on these systems depend on their functional state (5), being marked on the scarcely activated systems and scarce on the markedly activated ones. The obtained data showed that the lower doses increased the head witch response induced by L-5-HTP, whereas the higher doses inhibited this behavioral effect, which is a measure of serotonergic activation (3,20). Thus, it appeared that low doses of isradipine or darodipine could further enhance the activated neurotransmission, whereas the inhibitory effect of high doses prevailed in strongly activated systems. Moreover, the fact that the potency ratio between isradipine and darodipine was approximately 10 support the idea that their effects on the serotonergic systems could be due to VSCC blockade. In fact, a similar ratio exists

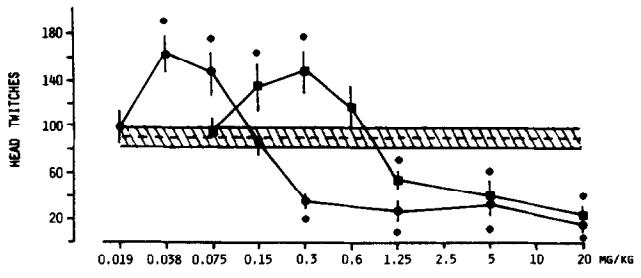

FIG. 2. Head twitch response induced by L-5-HTP (100 mg/kg, SC) in rats pretreated with different doses of isradipine (●) or darodipine (■). Mean values ± SEM of head twitch number exhibited in 90-min observation period. Dashed band represents the values ± SEM of saline-pretreated rats. $N = 6$–12 per group. $*p < 0.05$ in comparison to control animals (Mann-Whitney U-test).

TABLE 1

5-HTP AND 5-HIAA LEVELS AND THEIR RATIOS WITH 5-HT LEVELS IN DISCRETE BRAIN AREAS OF RAT TREATED WITH L-5-HTP

Brain Area	Pretreatment (IP)	Dose (mg/kg)	ng/g of Wet Weight		5-HTP/5-HT	5-HIAA × 100/5-HT
			5-HTP	5-HIAA		
Brain stem	Vehicle	–	6492 ± 222	1938 ± 83	5.20 ± 0.04	155 ± 2.7
	Isradipine	0.05	5931 ± 363	2089 ± 157	4.85 ± 0.29	171 ± 12
		1.50	6749 ± 188	1778 ± 67	5.35 ± 0.10	141 ± 2.3*
	Vehicle	–	6746 ± 760	2058 ± 270	5.52 ± 0.51	176 ± 32
	Darodipine	0.3	4146 ± 530†	3455 ± 276†	3.85 ± 0.40‡	330 ± 35†
		5.0	8425 ± 243§	1657 ± 27§	7.15 ± 0.23‡	141 ± 2.4§
Hippocampus	Vehicle	–	8363 ± 197	1300 ± 49	11.7 ± 0.21	171 ± 4.5
	Isradipine	0.05	7915 ± 414	1512 ± 129	11.0 ± 0.40	212 ± 21
		1.50	8505 ± 166	1167 ± 37*	12.0 ± 0.36	164 ± 4.0*
	Vehicle	–	7426 ± 836	1607 ± 365	10.4 ± 0.92	243 ± 70
	Darodipine	0.3	4422 ± 707‡	3044 ± 267†	6.1 ± 0.73†	443 ± 58‡
		5.0	8758 ± 333§	1042 ± 59*	12.3 ± 0.64§	147 ± 10§
Striatum	Vehicle	–	4868 ± 145	5398 ± 185	1.70 ± 0.03	188 ± 2.8
	Isradipine	0.05	4537 ± 185	5420 ± 134*	1.64 ± 0.06	196 ± 9.4
		1.50	5333 ± 393	4735 ± 183‡	1.92 ± 0.13	171 ± 2.2*
	Vehicle	–	4649 ± 592	5316 ± 271	1.70 ± 0.12	214 ± 37
	Darodipine	0.3	3029 ± 658	6340 ± 502	1.40 ± 0.16	350 ± 69
		5.0	5779 ± 240§	4934 ± 201*	2.04 ± 0.12*	173 ± 6.4*

Values are means of five rats ± SEM. The rats were given isradipine or darodipine 130 or 90 min, respectively, before killing. Forty minutes after isradipine or immediately after darodipine, the rats received IP carbidopa 25 mg/kg. L-5-HTP was SC administered at a dose of 20 mg/kg, 60 min before killing.

*Significantly different from the group treated with the other drug dose (orthogonal comparison), $p < 0.05$.

†Significantly different from control (two-tailed Dunnett's t-test), $p < 0.01$.

‡Significantly different from control (two-tailed Dunnett's t-test), $p < 0.05$.

§Significantly different from the group treated with the other drug dose (orthogonal comparison), $p < 0.01$.

(26) between the affinity for specific binding sites (i.e. VSCC) of the two drugs whereas no gross differences have been found between their distribution to the brain (28). The biochemical data from rats treated with L-5-HTP fully agreed with the observed behavioral data: biochemical effects of isradipine show a similar trend to the darodipine-induced effects, which were particularly univocal. In fact, the lower dose of the latter drug increased both consumption of the 5-HT precursor and production of the neurotransmitter metabolite, decreasing or leaving unchanged the neuronal 5-HT content. This strongly suggested facilitation of neurotransmitter release and increased serotoninergic neurotransmission, which could account for the enhancement of head twitch response. On the contrary, the higher dose of darodipine reduced both consumption of 5-HTP and production of 5-HIAA, leaving unchanged the neuronal 5-HT content. Therefore, it appeared that the studied drugs at the higher dose inhibited 5-HTP decarboxylation and/or serotonin release, which could account for the reduced behavioral response to L-5-HTP administration.

The central effects of darodipine appeared to be rather selective in view of the fact that isradipine is much more effective than darodipine on the cardiovascular apparatus (2). On this basis, it also could be assumed that peripheral effects of the studied drugs did not play a role on their central effects. On the other hand, both isradipine and darodipine were particularly effective in the hippocampus, where the highest density of their specific binding sites had been found (6,26). The pattern of distribution of both darodipine and isradipine binding sites in the rat brain is identical to that of nitrendipine, another 1,4-dihydropyridine with high affinity and selectivity for L-type VSCC (15). Indeed, this well-known class of channels is presently defined as dihydropyridine sensitive to distinguish them from T-, N-, and P-type VSCC, which are dihydropyridine resistent (21,26).

All these considerations support the idea that the studied compounds, and perhaps other calcium antagonists, could modulate the serotonergic neurotransmission by inhibiting the neuronal calcium influx through the L-type brain VSCC. The present data, being preliminary, do not allow any explanation of the differences in the effects between lower and higher doses of the studied compounds. Studies are in progress utilizing specific serotonergic agonists to better understand the intimate mechanisms underlying the observed effects.

In conclusion, peripherally administered isradipine or darodipine appeared to activate the serotonergic turnover in the rat brain, showing a peculiar profile of effects. The effects on 5-HT turnover depend on enhancement of serotonergic neurotransmission, especially when the drugs were administered at the lowest doses. Increasing the dose, both isradipine and darodipine also displayed inhibition of 5-HT synthesis and release, which could predominate when the serotonergic systems were strongly activated. All these effects appeared to be due to VSCC blockade into the brain, with darodipine more effective and selective than isradipine.

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