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Interactions Between Darodipine or Isradipine and the 5-HT_1A Receptor Agonist 8-OHDPAT in Rat Brain

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GAGGI, R., R. D'ALLOLIO, M. SANTANGELO AND P. RONCADA. *Interactions between darodipine or isradipine and the 5-HT_1A receptor agonist 8-OHDPAT in rat brain.* PHARMACOL BIOCHEM BEHAV **58**(2) 299–303, 1997.—Isradipine and darodipine are dihydropyridine calcium antagonists that affect the serotonergic pathways with a peculiar profile of effects because, at low dose (0.08 and 0.3 mg/kg, respectively) they facilitate, but at high dose (1.60 and 5.0 mg/kg, respectively) they inhibit the serotonergic neurotransmission. To investigate the mechanisms of these effects, the selective 5-HT_1A receptor agonist 8-OHDPAT was injected SC to rats pretreated IP with isradipine (0.04–1.60 mg/kg) or darodipine (0.3–5.0 mg/kg). By stimulating presynaptic 5-HT_1A autoreceptor, 8-OHDPAT induced signs of inhibition of the serotonergic neurotransmission (i.e., decrease of the 5-HIIA/5-HT ratio), but it also produced behavioral effects by stimulating postsynaptic 5-HT_1A receptors (i.e., forepaw treadings). A low dose of isradipine (0.08 mg/kg) or darodipine (0.3 mg/kg) antagonized the presynaptic, but enhanced the postsynaptic effects of 8-OHDPAT, suggesting relief of the autoreceptor-mediated inhibition of the 5-HT release. Thus, the amine released could stimulate postsynaptic receptors, adding its action to that of 8-OHDPAT. A high dose of isradipine (1.60 mg/kg) or darodipine (5.0 mg/kg) left unchanged, or also enhanced, the signs of inhibition of serotonergic neurotransmission displayed by 8-OHDPAT, reducing but not suppressing the increase in the behavioral response to the stimulation of postsynaptic 5-HT_1A receptors. It was speculated that the effects of isradipine and darodipine on serotonergic pathways of rat brain could be due to changes in the back-regulation of the neurotransmission, mediated by 5-HT_1A autoreceptors. This mechanism of action could be extended to other dihydropyridine calcium antagonists, because blockade of L-type VSCC by these compounds appears to be involved in their effects on brain 5-HT turnover. © 1997 Elsevier Science Inc.

Dihydropyridine calcium antagonists Rat brain areas Serotonin and metabolite Forepaw treading 5-HT_1A receptors 8-OHDPAT

PREVIOUS studies showed that the peripheral administration of calcium-channel antagonists, especially those belonging to the dihydropyridine class, affect brain serotonin (5-HT) metabolism, suggesting that they increase the neurotransmitter turnover in various brain areas (3,5,9,10). In fact, when injected intraperitoneally to rats, these drugs enhance the levels of the 5-HT metabolite, 5-hydroxyindole-3-acetic acid (5-HIIA), and/or the 5-HIIA/5-HT ratio. Darodipine (13) and isradipine (14) are potent compounds (4,19) that easily pass the blood–brain barrier (21) and display a peculiar profile of effects (7): at low doses (e.g., 0.08 mg/kg of isradipine or 0.3 mg/kg of darodipine), they act as other dihydropyridines, whereas at high doses (e.g., 1.60 mg/kg of isradipine or 5.0 mg/kg of darodipine), they inhibit the 5-HT turnover. The changes in the transmitter metabolism appear to be related to effects on serotonergic neurotransmission, because low doses of darodipine or isradipine increased, whereas high doses of these drugs inhibited, the head-twitch response to the L-5-hydroxytryptophan administration (7), which is a measure of serotonergic activation (2,16). However, the mechanisms underlying the effects of the calcium antagonists on the serotonergic pathways are quite unknown, although blockade of the L-type

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neuronal voltage-sensitive channel (VSCC) appears to be involved (5,7,10). Previous data suggest (7) that dihydropyridine calcium antagonists, similar to the low doses of darodipine or isradipine, could inhibit the function of 5-HT autoreceptors. These presynaptic receptors, mostly belonging to the 5-HT_1A type, regulate both the synthesis and release of 5-HT (15,22), especially in the neurones of the raphe dorsal and median nuclei, where they display very high density (17). However, other 5-HT_1A receptors, being located postsynaptically in various brain areas, appear to be involved in the behavioral effects of 5-HT_1A agonists. In particular, the forepaw treadings are believed (20) to be due to direct stimulation of postsynaptic 5-HT_1A receptor by 5-HT_1A agonists.

Stimulating presynaptic 5HT_1A autoreceptors, the selective agonist 8-hydroxy-2-(di-N-propylamino)-tetralin (8-OHDPAT) would change the 5-HT and 5-HIIA brain content and the 5-HIIA/5-HT ratio, this depicting inhibition of the serotonergic neurotransmission (6). On the other hand, 8-OHDPAT produces forepaw treadings acting on postsynaptic 5-HT_1A receptors (20). Treatment with low or high doses of darodipine or isradipine before giving 8-OHDPAT offered the opportunity to gain insight into the actions of calcium antagonists on the function of 5-HT_1A receptors. Darodipine and isradipine can modify the 5-HT and 5-HIIA brain content, but it is not known if a change in the functionality of the 5-HT_1A autoreceptors occurs. Nevertheless, the present data do not disagree with the hypothesis that the blockade of L-type VSCC could modify the function of 5-HT_1A autoreceptors.

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) and free access to water and food.

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

Drugs and Treatments

8-OHDPAT hydrobromide (Sigma Inc., St. Louis, MO, USA) was dissolved with saline and administered SC in a volume of 1 ml/kg. Darodipine and isradipine (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 kilogram of body weight was contained in 4 ml of suspension, that was administered IP. The time between darodipine administration and sacrifice of the animals was shorter than that for isradipine because the effects of the lat-

TABLE 1

5-HT AND 5-HIIA LEVELS IN DISCRETE BRAIN AREAS OF RATS PRETREATED WITH SALINE, VEHICLE, DARODIPINE OR ISRADIPINE AND TREATED WITH 8-OHDPAT OR SALINE

Brain areas	Pretreatment (mg/kg IP)	Treatment (SC)	5-HT	5-HIIA	5-HIIAx100/5-HT
Brain stem	Saline	Saline	633 ± 4	414 ± 15	65.4 ± 2.5
	Vehicle	8-OHDPAT	814 ± 25**	360 ± 22	44.1 ± 1.7**
	Darodipine (0.3)	8-OHDPAT	781 ± 26	368 ± 16	47.1 ± 0.9
	Darodipine (5.0)	8-OHDPAT	778 ± 18	348 ± 11	44.8 ± 1.2
	Isradipine (0.08)	8-OHDPAT	817 ± 10	407 ± 6	49.8 ± 1.1*
	Isradipine (1.60)	8-OHDPAT	872 ± 30	393 ± 9	45.1 ± 0.9†
Hippocampus	Saline	Saline	396 ± 12	303 ± 11	76.7 ± 1.5
	Vehicle	8-OHDPAT	515 ± 21**	275 ± 8	53.6 ± 1.0**
	Darodipine (0.3)	8-OHDPAT	460 ± 18	280 ± 8	61.3 ± 2.3*
	Darodipine (5.0)	8-OHDPAT	477 ± 21	260 ± 13	54.5 ± 1.1†
	Isradipine (0.08)	8-OHDPAT	514 ± 14	302 ± 6	58.9 ± 0.9*
	Isradipine (1.60)	8-OHDPAT	540 ± 7	269 ± 4†	49.8 ± 1.3†
Striatum	Saline	Saline	665 ± 4	535 ± 5	80.6 ± 1.1
	Vehicle	8OHDPAT	664 ± 24	497 ± 18	74.9 ± 1.0
	Darodipine (0.3)	8-OHDPAT	715 ± 27	564 ± 21	79.0 ± 1.1
	Darodipine (5.0)	8-OHDPAT	646 ± 27	473 ± 28†	73.0 ± 1.7
	Isradipine (0.08)	8-OHDPAT	691 ± 21	563 ± 13	81.7 ± 2.8*
	Isradipine (1.60)	8-OHDPAT	661 ± 13	481 ± 13†	72.7 ± 1.4†
F.P. Cortex	Saline	Saline	270 ± 7	162 ± 10	60.2 ± 3.5
	Vehicle	8-OHDPAT	309 ± 27	162 ± 15	52.5 ± 1.8**
	Darodipine (0.3)	8-OHDPAT	312 ± 13†	181 ± 9	57.8 ± 1.0†
	Darodipine (5.0)	8-OHDPAT	392 ± 16*	168 ± 11	43.1 ± 2.4*
	Isradipine (0.08)	8-OHDPAT	296 ± 11	176 ± 4	59.8 ± 2.6*
	Isradipine (1.60)	8-OHDPAT	349 ± 8	166 ± 3	47.5 ± 0.7†

Values are means of five rats ± SEM. The animals were given darodipine or isradipine 60 or 90 min, respectively, before killing. Thirty minutes before killing, 8-OHDPAT 0.5 mg/kg or saline was SC administered to all the rats.

**Significantly different when compared to the group prereated and treated with saline (two-tailed Dunnett's *t*-test.), $p < 0.05$.

*Significantly different from the group pretreated with vehicle and treated with 8-OHDPAT (two-tailed Dunnett's *t*-test), $p < 0.05$.

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

ter drug had been found to be longer lasting than those of darodipine (1).

First Experiment: Effects of the Pretreatment with Darodipine or Isradipine on the 8-OHDPAT-induced Changes in the 5-HT and 5-HIIA Levels in Discrete Brain Areas

Groups of five rats were injected IP with vehicle, darodipine (0.3 or 5.0 mg/kg), or isradipine (0.08 or 1.60 mg/kg). Sixty minutes after isradipine, or 30 min after vehicle or darodipine, 8-OHDPAT (0.5 mg/kg) was administered SC to all the rats, which were sacrificed 30 min later. Another group of five rats was pretreated IP with saline before receiving saline SC.

Second Experiment: Effects of the Pretreatment with Darodipine or Isradipine on the 8-OHDPAT-induced Forepaw Treadings

The rats (n = 6–12 per group) were habituated to the experimental cages (38 × 30 × 25 cm, transparent plexiglas) for 30 min before receiving 8-OHDPAT (0.5, 1, or 2 mg/kg SC) or saline. After 10 min, observers who were unaware of the treatments counted the number of forepaw treadings exhibited by the animals in 1 h. Different groups of rats (n = 6–12 per group) were pretreated with isradipine (0.04, 0.08, 0.15, or 1.25 mg/kg) or darodipine (0.3, 0.6, 1.25, or 5.0 mg/kg) 30 min or immediately before, respectively, the habituation period in the experimental cages. The animals were then treated with 0.5 mg/kg of 8-OHDPAT and observed for the forepaw treadings as described above. A control group of 12 rats was pretreated with the vehicle before receiving 0.5 mg/kg of 8-OHDPAT.

Analytical Procedure

All the rats were decapitated in the afternoon (1600–1800) to avoid circadian variations in the brain serotonin and metabolite content. The brain was removed rapidly and ice cooled immediately. Olfactory tubercles and cerebellum were discarded, whereas hypothalamus, hippocampus, brain stem (pons + medulla oblongata), striatum, and fronto-parietal cortex 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. Serotonin and 5-HIAA were determined simultaneously by high performance liquid chromatography with electrochemical detection following the method of Seegal et al. (18), modified as described previously (8) in detail. The method permits quantification of 50–100 pg of 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. Orthogonal comparison between the lower and the higher dose was also performed in the first experiment.

Behavioral data (number of forepaw treadings exhibited by the animals in the 60-min observation period) were analyzed by the Mann–Whitney U-test.

RESULTS

As expected, 8-OHDPAT induced both signs of inhibition of 5-HT turnover (Table 1) and its peculiar behavioral response, i.e., forepaw treadings (Fig. 1). At the dose of 0.5 mg/kg, 8-OHDPAT significantly decreased the 5-HIIA/5-HT ratio in all brain areas (Table 1), with the possible exception of the striatum, where the changes were not statistically significant. The decrease was due to enhancement of the 5-HT levels, whereas the 5-HIAA tissue content remained almost unchanged. However, it is known (6) that doses of 8-OHDPAT higher than 0.5 mg/kg, will further decrease the 5-HIIA/5-HT ratio by reducing the tissue metabolite levels, too.

Pretreatment with isradipine or with darodipine, although to a lesser extent, appeared to induce quite different effects according to the dose (Table 1). In general, the lower dose of the two drugs tended to inhibit, whereas the higher dose tended to enhance the effects of 8-OHDPAT on the 5-HIIA/5-HT ratio. In particular, 0.3 mg/kg of darodipine significantly inhibited, $t(5,24) = 3.79$, $p < 0.01$, the decrease of the ratio in the hippocampus, whereas 5.0 mg/kg did not. The difference in the effects of the two drug doses was statistically significant, $F(1,24) = 11.20$, $p < 0.01$. In the fronto-parietal cortex, the higher dose of darodipine further decreased, $t(5,24) = 3.78$, $p < 0.01$, the metabolite/amine ratio, which was modestly enhanced by the lower dose. However, the difference between the two drug doses was highly significant, $F(1,24) = 35.23$, $p < 0.01$. The data regarding darodipine effects in hypothalamus (not shown), brain stem, and striatum did not show statistically significant differences.

As far as isradipine effect is concerned, pretreatment with both the lower and the higher dose induced similar effects in all the brain areas (Table 1), except in the hypothalamus (data not shown), where the drug appeared to be ineffective. Isradipine 0.08 mg/kg inhibited the 8-OHDPAT-induced decrease in the 5-HIIA/5-HT ratio, whereas 1.60 mg/kg did not affect or also enhanced the effect of the selective 5-HT_1A receptor agonist. In each brain area, the lower dose of isradipine displayed significantly different effects from those of the higher dose.

As concerns the forepaw treadings induced by 0.5 mg/kg of 8-OHDPAT, both darodipine and isradipine enhanced this behavioral response, the latter being at least 10 times more

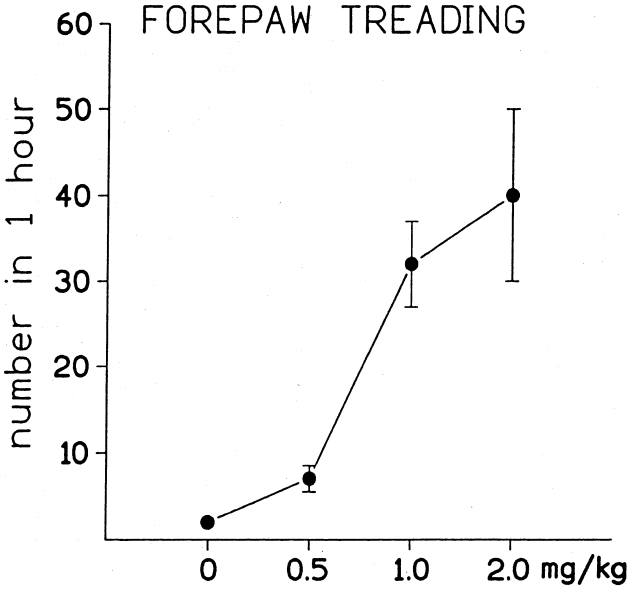

FIG. 1. Forepaw treadings induced by different doses of 8-OHDPAT during 1-h observation period. Mean values ± SEM. n = 6–12 per group.

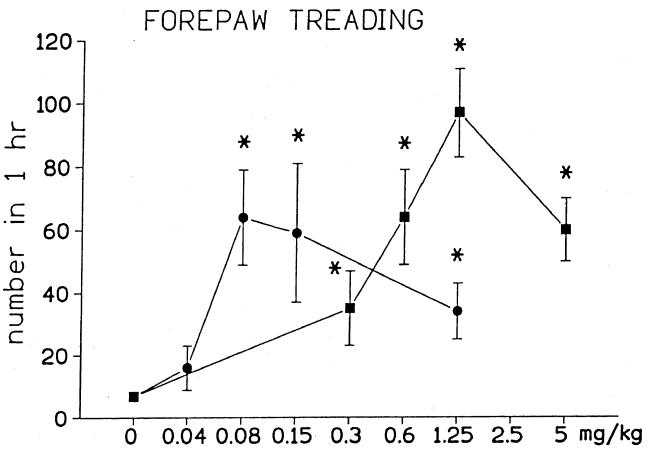

FIG. 2. Forepaw treadings induced by 0.5 mg/kg of 8-OHDPAT in animals pretreaded with different doses of isradipine (circles) or darodipine (squares) during 1-h observation period. Mean values ± SEM. $n = 6–12$ per group. $*p < 0.05$ in comparison to group treated with 8-OHDPAT alone (Mann–Whitney *U*-test).

potent than the former. However, this effect increased until the dose remained in the range 0.04–0.08 mg/kg of isradipine or 0.3–1.25 mg/kg of darodipine, whereas it began to decrease when the doses of both the drugs exceded the above-mentioned limits (Fig 2.).

CONCLUSIONS

As already reported (6), the SC administration of 8-OHDPAT 0.5 mg/kg was sufficient to induce the peculiar effects of the stimulation of both presynaptic and postsynaptic 5-HT_1A receptors. Acting on the 5-HT_1A autoreceptors, the drug decreased the 5-HIIA/5-HT ratio markedly, chiefly by inhibiting the release of neurotransmitter (12) that accumulates especially in the brain stem and hippocampus. It is known that doses of 8-OHDPAT higher than 0.5 mg/kg do not change the 5-HT tissue content, whereas they decrease the 5-HIIA levels markedly, so that the 5-HIIA/5-HT ratio continues to decrease. This could be explained with both an increasing inhibition of 5-HT release (12) and inhibition of the 5-HT synthesis (11). The behavioral response, being due to direct stimulation by 8-OHDPAT of postsynaptic 5-HT_1A receptor, cannot be blocked by presynaptic inhibition of serotonergic neutransmission. However, as the number of forepaw treadings increases progressively in the dose range between 0.5 and 2 mg/kg of 8-OHDPAT, each synergistic interaction with 5-HT_1A agonist could potentiate the effect of the low dose of the drug. It could be argued that the 5-HT released by terminals of serotonergic neurones adds its effect to that of 8-OHDPAT, by contributing to the stimulation of postsynaptic 5-HT_1A receptors. Therefore, even a partial relief of the 5-HT release-inhibiting effect mediated by 5-HT_1A receptors could enhance the number of forepaw treadings produced by 8-OHDPAT. This could explain the enhancement of the behavioral response to the 5-HT_1A agonist in rats pretreated with the lower dose of darodipine or isradipine. In various brain areas, these rats showed 5-HT and 5-HIIA levels and 5-HIIA/5-HT ratios that suggest marked relief of the 8-OHDPAT-induced inhibition of serotonergic neurotransmission. Because darodipine and isradipine show very low affinity for monoamine receptors (4), direct interactions between these drugs and 5-HT autoreceptors should be excluded. Thus, it was hypothesized that blockade of L-type VSCC antagonizes the 5-HT_1A-mediated back-regulation of the serotonergic neurotransmission. The involvement of L-type VSCC is supported by the fact that isradipine was effective at doses 10 or more times lower than those of darodipine, the affinity for neuronal L-type VSCC of the latter drug being at least 10 times lower than that of the former one (19).

It was already shown (7) that high doses of both darodipine and isradipine also displayed inhibitory effects, which prevailed when serotonergic systems are strongly activated. Consistently, the present data show that the administration of the higher dose of darodipine or isradipine did not antagonize, or also enhanced, the effects of 8-OHDPAT on the 5-HT and 5-HIAA levels and the 5-HIIA/5-HT ratio of various brain areas. In any case, the effects of the higher dose of the two drugs on brain 5-HT metabolism were significantly different from those of the lower dose. However, rats pretreated with darodipine 5.0 mg/kg, or isradipine 1.25 mg/kg, still displayed increased (but under maximal) behavioral response to 8-OHDPAT 0.5 mg/kg. This discrepancy could be due to the fact that the biochemical data depicted the functional situation of serotonergic pathways fixed at the time of rats killing, whereas the behavioral response resulted from a continuous train of functional changes in the serotonergic neurotransmission during the whole observation period. Thus, the number of forepaw treadings could be enhanced even by doses of darodipine or isradipine that have not antagonized, or also have increased, the biochemical markers of inhibition of the serotonergic neurotransmission.

In conclusion, the present work further supports the hypothesis (7) that darodipine and isradipine, acting on L-type VSCC, could modulate the neurotransmission in the seroto–nergic pathways by affecting the back-regulation of neuronal activity. Possible postsynaptic actions of these drugs cannot be excluded, but the present data do not allow any speculation about this question, except that, if such actions exist, they should be opposite to these above mentioned, i.e., increasing at low doses the response to the stimulation of postsynaptic 5-HT_1A receptors.

Further studies are going to ascertain differences with other dihydropyridine compounds as well as help to better understand the mechanisms underlying the actions of the calcium antagonists on the serotonergic neurotransmission. In this regard, in our laboratory, we are pursuing studies with drugs enhancing 5-HT in the synaptic cleft, such as imipramine and fluoxetine, which may be expected to potentiate both the 8-OHDPAT-induced forepaw-treading and the changes in the serotonergic neurotransmission induced by low doses of dihydropyridine calcium antagonists. The possible actions of these drugs on postsynaptic 5-HT_1A receptors would be evaluated by pretreating the animals with a specific 5-HT_1A antagonist.

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