Peripheral Dopamine Receptors in the Antihypertensive Action of Dihydroergotoxine in Humans

GIUSEPPE MERCURO, ZVANI L. ROSSETTI, CARLO A. RIVANO, MASSIMO RUSCAZIO, LILIANA TOCCO, GIANNI LUIGI GESSA, AND ANGELO CHERCHI

SUMMARY The effect of the intravenous administration of dihydroergotoxine (6 μg/kg) on arterial blood pressure, heart rate, and plasma concentrations of norepinephrine and 3,4-dihydroxyphenylacetic acid (the deaminated dopamine metabolite) was studied in 20 subjects with essential hypertension (8 men and 12 women aged 32-68 years old, World Health Organization Class I-II). In supine resting subjects, dihydroergotoxine significantly decreased systolic blood pressure (from 175 ± 5 to 156 ± 4 mm Hg; p<0.001), diastolic blood pressure (from 109 ± 4 to 95 ± 3 mm Hg; p<0.001), and heart rate (from 71 ± 2 to 63 ± 2 beats/min; p<0.001) as compared with the results of placebo treatment. Moreover, dihydroergotoxine reduced plasma levels of norepinephrine (from 368 ± 39 to 238 ± 33 pg/ml; p<0.001) and 3,4-dihydroxyphenylacetic acid (from 1.57 ± 0.21 to 1.22 ± 0.13 ng/ml; p<0.01). The time course of the blood pressure decrease paralleled that of plasma norepinephrine concentration. Dihydroergotoxine did not suppress the cardiovascular and plasma norepinephrine response to standing. The effect of domperidone, a peripheral presynaptic dopamine receptor antagonist, on dihydroergotoxine response was studied in six of the 20 subjects (3 men and 3 women 48-64 years old). The intravenous administration of domperidone (0.3 mg/kg) prevented the dihydroergotoxine-induced reduction in blood pressure and heart rate and the fall in plasma norepinephrine and 3,4-dihydroxyphenylacetic acid levels. Domperidone administered alone failed to significantly modify any measured variables. These results suggest that the antihypertensive effect of dihydroergotoxine can be mediated by the inhibition of norepinephrine release from peripheral sympathetic nerves secondary to the activation of presynaptic dopamine receptors.

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KEY WORDS • peripheral dopamine presynaptic receptors • plasma 3,4-dihydroxyphenylacetic acid level • blood pressure • dopamine agonists • domperidone

MANY ergot derivatives possess hypotensive properties, both in experimental animals and in humans. In particular, bromocriptine reduces arterial blood pressure in normal and hypertensive subjects. This effect has been attributed to the stimulation of dopamine receptors of the DA2 subtype located on peripheral sympathetic nerve endings, whose activation causes an inhibition of norepinephrine release. Accordingly, the administration of bromocriptine produces a decrease in plasma norepinephrine concentration temporally correlated to the decrease in blood pressure, an effect prevented by administration of domperidone, a selective DA2 receptor antagonist that does not penetrate the blood-brain barrier.

Dihydroergotoxine mesylate, a mixture of the dihydrogenated derivatives of the four peptide alkaloids ergocornine, ergocristine, α-ergocryptine, and β-ergocryptine, also interacts with dopamine receptors and possesses antihypertensive properties. A recent report on spontaneously hypertensive rats suggests that the antihypertensive effect of dihydroergotoxine in this species may be mediated by a peripheral dopaminergic mechanism. The present study was aimed at clarifying whether
the antihypertensive effect of dihydroergotoxine is also mediated in humans by the stimulation of peripheral dopamine receptors. Accordingly, we studied the effect of dihydroergotoxine on arterial blood pressure, heart rate, and plasma concentration of norepinephrine and 3,4-dihydroxyphenylacetic acid (DOPAC), the deaminated dopamine metabolite, in patients with essential hypertension.

Dihydroergotoxine was found to induce a parallel decrease in norepinephrine and DOPAC plasma concentrations and in blood pressure and heart rate. These effects were prevented by domperidone. These findings suggest that the antihypertensive effect of dihydroergotoxine is due to the inhibition of norepinephrine release secondary to the stimulation of peripheral DA₂ receptors.

Materials and Methods
Subjects and Experimental Protocol
A group of 20 outpatients with stabilized, essential hypertension (World Health Organization Class I–II) was recruited for this study. Volunteer participation was based on informed consent. The study was approved by the institution’s medical research control committee. Physical examination, electrocardiogram, and routine laboratory tests showed no evidence of renal and hepatic disease or secondary causes of hypertension. All patients were drug-free for at least 2 weeks before the study began.

In the first session all 20 subjects (8 men and 12 women aged 32–68 years; mean age, 50 ± 3 years) received dihydroergotoxine mesylate (Hydergine; Sandoz A.G., Basel, Switzerland), 6 µg/kg, or placebo (saline) by a 5-minute intravenous infusion according to a randomized, double-blind, crossover protocol. The influence of domperidone on dihydroergotoxine response was investigated in a group of six of the same hypertensive subjects, all of whom responded to dihydroergotoxine in the first session (3 men and 3 women aged 48–64 years; mean age, 57 ± 3 years), using a double-blind, placebo-controlled, Latin-square design. Each subject received in three different sessions: 1) domperidone (Motilium; Janssen Pharmaceutica, Beerse, Belgium), 0.3 mg/kg i.v., in 3 minutes, plus dihydroergotoxine, 6 µg/kg i.v. in 5 minutes; 2) domperidone plus placebo; and 3) placebo plus placebo. The second drug followed the first by 20 minutes. Sessions were at least 4 days apart.

During the 7 days preceding the experiments, all the patients were maintained on a constant diet containing 150 mEq sodium and 60 mEq potassium. They were asked to refrain from smoking and drinking alcohol, tea, or coffee for at least 48 hours before each experiment.

At approximately 1000, an 18-gauge Teflon cannula was inserted in an antecubital vein and kept patent by a polyethylene obturator. Heparin was not used. After at least 30 minutes of acclimatization in a quiet, semidark room at a controlled temperature of 20°C, subjects’ basal blood pressure and heart rate were measured and an 8-ml blood sample was taken during supine rest and again after subjects had spent 5 minutes in an unsupported upright posture. Dihydroergotoxine or placebo infusion was started after a second 30-minute period of supine rest. Heart rate was measured from the electrocardiogram; arterial blood pressure was recorded by a cuff and mercury sphygmomanometer. Blood specimens were obtained without venous stasis. In the first experiment blood samples were collected 10, 20, 30, 60, 90, and 120 minutes after the beginning of dihydroergotoxine or placebo infusion. At 120 minutes, a second sampling with the subjects in the upright posture was taken. In the second experiment, the samples were collected during supine rest, 20 minutes after the first treatment, and 10, 30, 60, and 90 minutes after the second treatment. Blood pressure and heart rate were recorded just before the collection of each sample, in both the first and the second experiment. Each blood pressure value was the average of three measurements taken by the same examiner. Diastolic blood pressure was measured as Phase 5 (disappearance of sounds).

Sample Processing
All samples were placed in iced tubes containing 50 µl of 2% EDTA (wt/vol) and immediately centrifuged at 4°C; the plasma was stored at -75°C until analysis. Norepinephrine and DOPAC plasma concentrations were assayed by high-performance liquid chromatography with electrochemical detection, using a previously described extraction procedure with a slight modification. The chromatographic system consisted of a Waters M-510 delivery system, an M-730 data module, a WISP 710 B automatic injector, an M-721 system controller (Waters Associates, Milford, MA, USA) and a BAS LC-4B amperometric detector (Bioanalytical Systems, West Lafayette, IN, USA) equipped with a glassy carbon working electrode (TL-5, Bioanalytical Systems). The column was a Supelco deactivated RP C-18 with an outside diameter of 250 x 4 mm (Supelco, Bellefonte, PA, USA); the mobile phase was 0.1 M sodium acetate, pH 4.9, containing EDTA, 50 mg/L, as the ion pairing reagent, and 5% methanol. The flow rate was maintained at 0.8 ml/min. The applied potential was set to 0.70 V against an Ag/AgCl reference electrode (Bioanalytical Systems). Interassay variability was ±5.4%. The detection limit of assays for norepinephrine and DOPAC was about 40 pg/ml of plasma.

Statistical Analysis
All statistics were handled by a Sirius 9000 microcomputer (Sirius Systems Technology, Scotts Valley, CA, USA). Results are given as the mean ± SEM. The statistical significance of the changes was calculated by a two-way analysis of variance and Student’s t test for paired data, as appropriate. The changes were considered significant at a p level less than 0.05.
Results

Table 1 compares the responses of blood pressure, heart rate, and plasma norepinephrine and DOPAC concentrations to the infusion of placebo and dihyd ergotoxine at the peak drug effect. Values refer to hypertensive subjects during supine rest and after 5 minutes of standing. A significant response to dihyd ergotoxine was observed in 17 of the 20 subjects (85%). The three nonresponders were women. Values from these subjects have been included in the calculation of the means. No difference in the incidence of side effects was observed between responders and nonresponders. Namely, mild nausea was present in one responder and two nonresponders. Nasal congestion was seen in six responders and two nonresponders, and coldness of the extremities was noted in three responders. The placebo failed to significantly modify any measured variables. Dihyd ergotoxine maximally reduced systolic \( (p < 0.001) \) and diastolic blood pressure \( (p < 0.001) \) within 1 hour and heart rate \( (p < 0.001) \), plasma norepinephrine \( (p < 0.001) \) concentrations, and plasma DOPAC \( (p < 0.01) \) concentrations within 2 hours after treatment.

When subjects changed from a supine to a standing position, plasma norepinephrine level increased by approximately 50% and 60%, respectively, in placebo-treated and dihyd ergotoxine-treated subjects. However, the absolute norepinephrine concentration reached in dihyd ergotoxine-treated subjects in an upright position was significantly lower than that in control subjects \( (p < 0.01) \).

Figures 1 and 2 show the time course of dihyd ergotoxine effects on blood pressure, heart rate, and plasma norepinephrine and DOPAC concentrations. Dihyd ergotoxine significantly decreased, in comparison with placebo, systolic and diastolic blood pressure within a few minutes. Maximal effect was obtained at 30 minutes for systolic \( (156 \pm 4 \text{ vs } 175 \pm 5 \text{ mm Hg}; p < 0.001) \) and diastolic blood pressure \( (95 \pm 3 \text{ vs } 109 \pm 4; p < 0.001) \) and persisted up to 2 hours after treatment. The reduction in heart rate became significant 45 minutes after treatment \( (67 \pm 3 \text{ vs } 71 \pm 2 \text{ beats/min}; p < 0.01) \) and was more pronounced at 120 minutes \( (63 \pm 2 \text{ vs } 71 \pm 2 \text{ beats/min}; p < 0.001) \). A significant fall in plasma norepinephrine level occurred 30 minutes after dihyd ergotoxine infusion \( (260 \pm 42 \text{ vs } 356 \pm 37 \text{ pg/ml}; p < 0.01) \) and progressively increased at 90 minutes \( (227 \pm 23 \text{ vs } 341 \pm 36 \text{ pg/ml}; p < 0.001) \).

### Table 1. Effect of Acute Administration of Placebo (Saline) or Dihyd Ergotoxine (6 µg/kg i.v.) on Blood Pressure, Heart Rate, and Plasma Norepinephrine and 3,4-Dihydroxyphenylacetic Acid Levels in Subjects with Essential Hypertension

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal</th>
<th>Placebo</th>
<th>Dihyd ergotoxine*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>179 ± 4</td>
<td>175 ± 5</td>
<td>156 ± 4†</td>
</tr>
<tr>
<td>Standing</td>
<td>174 ± 4</td>
<td>180 ± 6</td>
<td>155 ± 4†</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>109 ± 3</td>
<td>109 ± 4</td>
<td>95 ± 3†</td>
</tr>
<tr>
<td>Standing</td>
<td>112 ± 2</td>
<td>116 ± 4</td>
<td>104 ± 2†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>74 ± 3</td>
<td>71 ± 2</td>
<td>63 ± 2†</td>
</tr>
<tr>
<td>Standing</td>
<td>85 ± 4</td>
<td>84 ± 4</td>
<td>71 ± 4†</td>
</tr>
<tr>
<td>Plasma NE (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>387 ± 39</td>
<td>371 ± 35</td>
<td>238 ± 33†</td>
</tr>
<tr>
<td>Standing</td>
<td>526 ± 43</td>
<td>552 ± 48</td>
<td>378 ± 46†</td>
</tr>
<tr>
<td>Plasma DOPAC (ng/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>1.6 ± 0.2</td>
<td>1.6 ± 0.2</td>
<td>1.2 ± 0.1†</td>
</tr>
<tr>
<td>Standing</td>
<td>1.5 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>1.3 ± 0.2</td>
</tr>
</tbody>
</table>

Values are means ± SEM of 20 subjects.  
BP = blood pressure; NE = norepinephrine; DOPAC = 3,4-dihydroxyphenylacetic acid. 
*Supine values at peak drug effect (within 1 hour for BP and 2 hours for HR, NE, and DOPAC). Standing values at 120 minutes after drug infusion. 
† \( p < 0.001 \), † \( p < 0.01 \), compared with corresponding placebo value.
Figure 2: Effect of infusion of placebo (saline) or dihydroergotoxine (6 µg/kg i.v.) on the plasma norepinephrine (NE) and 3,4-dihydroxyphenylacetic acid (DOPAC) concentrations in essential hypertensive subjects (n = 20) during supine rest. Vertical bars represent the SEM. Open triangle (p<0.05), filled triangle (p<0.01), and asterisk (p<0.001) indicate significant difference compared with placebo value.

Results of the second series of experiments in a subgroup of six essential hypertensive subjects are summarized in Table 2. The administration of domperidone before the dihydroergotoxine infusion prevented the lowering effect of dihydroergotoxine on heart rate and plasma norepinephrine and DOPAC concentrations. Moreover, the administration of dihydroergotoxine to the domperidone-treated subjects not only failed to decrease the blood pressure but also produced a progressive rise, which was significant 90 minutes after dihydroergotoxine infusion, in systolic (185 ± 9 vs 165 ± 3 mm Hg; p<0.05) and diastolic blood pressure (99 ± 3 vs 94 ± 2; p<0.05). In one subject the blood pressure increase was so marked as to require a prompt intravenous administration of furosemide. In contrast, no changes in the studied parameters were found after administration of domperidone alone.

The time course of effect of domperidone in combination with dihydroergotoxine, domperidone plus placebo, and placebo plus placebo on systolic and diastolic blood pressure is shown in Figure 3.

Discussion

Our results show that the intravenous administration of dihydroergotoxine produces a rapid and long-lasting fall in plasma norepinephrine and DOPAC concentrations, associated with a decrease in systolic and diastolic blood pressure and in heart rate. The changes in norepinephrine concentrations and the cardiocirculatory effects were temporally correlated. The finding that dihydroergotoxine did not suppress the standing-induced rise in plasma norepinephrine level is of practical and theoretical interest. Since this sympathetic response is essential for the maintenance of standing blood pressure, dihydroergotoxine failed to produce postural hypotension. A possible explanation for this finding is that the sensitivity of presynaptic dopamine receptor is reduced when the rate of neuronal firing is increased by standing. Accordingly, it has been recently reported that the sensitivity of dopamine autoreceptor in brain is inversely proportional to the firing rate of dopamine neurons.

Pretreatment with the selective DA2 receptor antagonist domperidone prevented both the cardiovascular response to dihydroergotoxine and its lowering effect on plasma norepinephrine level. Since domperidone, at the doses of 0.3 mg/kg used in this study, does not readily cross the blood-brain barrier, we ascribed the antihypertensive effect of dihydroergotoxine to the reduction of norepinephrine release from peripheral sympathetic nerves. In turn, the inhibition of norepinephrine to the domperidone-treated subjects not only failed to decrease the blood pressure but also produced a progressive rise, which was significant 90 minutes after dihydroergotoxine infusion, in systolic (185 ± 9 vs 165 ± 3 mm Hg; p<0.05) and diastolic blood pressure (99 ± 3 vs 94 ± 2; p<0.05). In one subject the blood pressure increase was so marked as to require a prompt intravenous administration of furosemide. In contrast, no changes in the studied parameters were found after administration of domperidone alone.

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nephrine release seems to depend on the stimulation of dopamine receptors, presumably located on noradrenergic nerve endings. In support of this hypothesis, binding studies and pharmacological interactions indicate that peripheral dopamine receptors of the D2 subtype are very similar to the central D2 receptor population\(^\text{16, 20}\) and that different ergot derivatives are agonists of such receptors.\(^\text{4}\) Accordingly, activation of peripheral D2 receptors has been proposed to explain the hypotensive effect of other ergot alkaloids, such as bromocriptine, lergotrile, and pergolide.\(^\text{1-5, 8}\) In addition, we have recently shown that bromocriptine reduces plasma norepinephrine levels in normotensive and especially in hypertensive subjects\(^\text{3}\) and that this effect is prevented by domperidone.\(^\text{9}\) The finding that pretreatment with domperidone not only prevented the lowering effect of dihydroergotoxine on blood pressure but also actually caused a hypertensive response suggests that dihydroergotoxine, besides inhibiting norepinephrine release, exerts an intrinsic vasoconstrictor effect on vascular smooth muscles similar to that of other ergot alkaloids.\(^\text{13, 21}\) an effect that is normally masked by its presynaptic action. Irrespective of the mechanism involved, however, the hypertensive response to dihydroergotoxine after domperidone treatment calls for some caution when such a drug combination is used in clinical practice.

The changes in plasma concentration of DOPAC in response to dihydroergotoxine are difficult to interpret. In fact, the origin and importance of this dopamine metabolite in plasma are not yet clear. DOPAC might originate from intraneuronal deamination of dopamine in central dopamine neurons\(^\text{22}\) as well as in peripheral dopaminergic neurons.\(^\text{23, 24}\) Alternatively, plasma DOPAC might reflect the intraneuronal deamination of dopamine in sympathetic nerve terminals, where dopamine serves as a precursor for norepinephrine.\(^\text{22-25}\)

The finding that about 25% of circulating DOPAC is decreased by dihydroergotoxine and that this effect is completely prevented by domperidone suggests that this DOPAC fraction is of peripheral origin. Conversely, these results suggest that dihydroergotoxine, at the doses used in the present study, fails to significantly stimulate central D2 receptors in controlling dopamine metabolism. If DOPAC originates from noradrenergic neurons, its decrease in plasma levels might reflect the inhibition of catecholamine synthesis within the noradrenergic neuron.

Experiments in progress in our laboratory have shown that the oral administration of 4.5 mg of dihydroergotoxine twice a day to 12 hypertensive patients has lowered blood pressure and plasma norepinephrine and that this effect is maintained for up to 6 months of treatment (unpublished observations, 1986).

In conclusion, our results provide further evidence for the existence in humans of dopamine inhibitory receptors controlling norepinephrine release and suggest that they mediate the antihypertensive effect of dihydroergotoxine.

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