Venodilating Action of Nipradilol (K-351) in the Pithed Rat Pretreated with Dihydroergotamine

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Abstract—The venodilating action of nipradilol was investigated by monitoring arterial blood pressure (BP), cardiac output (CO), heart rate (HR) and central venous pressure (CVP) in pithed rats treated with dihydroergotamine (DHE). DHE increased CVP and produced a simultaneous rise in BP and CO without appreciable changes in total peripheral resistance (TPR) and HR, indicating that DHE reduces venous capacity through venoconstriction. Nipradilol caused a fall in CVP, BP and CO without changing the TPR in the DHE-pretreated rat. By comparison, hydralazine reduced BP and TPR without changes in CO. Propranolol produced only a transient decrease in BP and TPR. These results indicate that nipradilol dilates venous capacitance vessels and thereby decreases cardiac filling pressure in animals with high venous tone, whereas hydralazine preferentially dilates resistance vessels.

Nipradilol (K-351), a new antihypertensive drug, has a long lasting antihypertensive action in various experimental hypertensive rats (1, 2). However, its hypotensive mechanisms in experimental animals appear to be complex because it is a β-adrenoceptor antagonist with a concomitant spasmolytic action and a weak (relative to its β-adrenoceptor blocking action) α-adrenoceptor blocking action (1). The spasmolytic property was demonstrated in isolated veins and arteries contracted by high KCl (1). The dilatation of veins, as capacitance vessels, would contribute to a fall in blood pressure (BP) by decreasing the cardiac filling pressure, resulting in a decrease in cardiac output (CO). In order to investigate the role of venodilatation in the hypotensive effect of nipradilol, we have used the dihydroergotamine (DHE)-treated pithed rat for this study. It has been reported that DHE causes a rise in BP and CO mainly by producing venoconstriction in the pithed rat (3). Since central sympathetic activity is eliminated in the pithed rat, and peripheral vascular resistance is very low, any α- and β-blocking action by nipradilol on heart and vessels would be minimized in this preparation.

Materials and Methods

Male Wistar rats weighing 350–400 g were lightly anesthetized with sodium pentobarbital (25 mg/kg, i.p.). Body temperature was kept at 37°C by external heating. During the experiments, all animals were subjected to artificial respiration via a tracheal cannula connected to a Harvard respirator (model 680) set to deliver 60 strokes/min. Tidal volume was adjusted to 18 ml/kg body weight. The central nervous system was destroyed by means of a blunt rod (diameter, 2.3 mm) inserted in the brain via the left orbit and then pushed backward as far as possible in the spinal canal. BP was measured through a catheter in the left common carotid artery using a pressure transducer (Statham, model P2311D). Heart rate (HR) was monitored with a cardiotachometer (Nihon Kohden, model AT-600G) which was triggered by the arterial pressure pulse. The chest was opened at the midline and an electromagnetic flow transducer (Nihon Kohden, model FR-020T or FR-025T) was placed around the aortic arch for measuring
Total peripheral resistance (TPR) was calculated by dividing mean arterial blood pressure (MABP) by CO.

Three pithed rats were used to measure central venous pressure (CVP), which was recorded via a Statham pressure transducer (model P231D) connected to a catheter inserted into the jugular vein and pushed forward into the superior vena cava.

All measurements were recorded on a thermal stylus recorder (Nihon Koden, model WT-683G). The rats were allowed to recover from anesthesia and surgical intervention for 1–1.5 hr. A femoral vein was cannulated for administering drug solutions.

The drugs used were dihydroergotamine tartrate (Sigma), nipradilol (K-351, Kowa), DL-propranolol hydrochloride (Sigma), and hydralazine hydrochloride (Tokyo Kasei). Nipradilol was dissolved in saline containing equimolar hydrochloride. Other drugs were dissolved in saline. All drugs were administered intravenously in a volume of 0.5 ml/kg body weight.

Statistical significance was calculated using Student's t-test or the modified t-test (Aspin-Welch method). The paired t-test was used when applicable. P values of less than 0.05 were considered to be significant. The data were expressed as the mean±S.E.M.

**Results**

Hemodynamic responses to DHE: The hemodynamic responses after administration of DHE (0.1 mg/kg) are displayed as actual tracings in a typical experiment (Fig. 1) and as summarized data obtained from 5 animals (Table 1). DHE produced a rapid, simultaneous increase in BP and CO within 1 min, and thereafter, both increased gradually up to 3 min. MABP and CO at 3 min were elevated 50.7±4.5% and 43.0±1.9% above the initial value, respectively. No change in BP was seen up to 10 min, whereas CO decreased gradually after 5 min. There was little increase in TPR during the first 5 min, but by 10 min, TPR was significantly elevated (Table 1). HR was unchanged.

Effect of nipradilol, hydralazine and propranolol in the presence of DHE: As mentioned above, between 2 and 10 min after administration of DHE (0.1 mg/kg), there were no remarkable changes in BP and CO, while a rise in TPR was seen only at 10 min. Therefore, all drugs were injected 3 min after DHE pretreatment. The initial

![Graph showing heart rate (HR) and arterial blood pressure (ABP) responses to DHE](image)

**Fig. 1.** Effects of DHE (0.1 mg/kg) on HR, BP and CO in the pithed rat. ABP: arterial blood pressure, MCO: mean cardiac output.
values of MABP, HR, CO and TPR before administration of saline, nipradilol, hydralazine and propranolol are presented in Table 2. Saline (0.5 ml/kg) was injected in control experiments.

Nipradilol, in doses of 0.3 and 1.0 mg/kg, reduced both MABP and CO in a dose-dependent manner in the DHE pretreated animal (Fig. 2). A decrease in MBP and CO occurred immediately after nipradilol, and these effects were sustained throughout the observation period. A dose of 1.0 mg/kg completely abolished the increase of MBP and CO produced by DHE. The magnitude of the decrease in MABP and CO was 15.2±2.3 mmHg and 6.0±2.4 ml/min at 2 min, respectively. Nipradilol did not significantly alter the gradual rise in TPR induced by DHE. HR was reduced slightly but significantly, being less than 5%.

Hydralazine (0.3 mg/kg) decreased MABP gradually and markedly, while CO was unchanged (Fig. 3). In association with the fall in MABP, TPR fell by 20% at 7 min. Appreciable changes in HR were not observed.

Propranolol (1.0 mg/kg) produced only a transient fall in MABP and TPR at 2 min of its administration (Fig. 3). HR decreased, but CO was unchanged.

**Effect of nipradilol on the elevated CVP**

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**Table 1. Effect of DHE (0.1 mg/kg) on MABP, HR, CO and TPR in the pithed rat**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>MABP (mmHg)</th>
<th>HR (beats/min)</th>
<th>CO (ml/min)</th>
<th>TPR (mmHg·min/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9</td>
<td>66.1±2.6</td>
<td>327.1±8.7</td>
<td>31.7±4.0</td>
<td>2.39±0.34</td>
</tr>
<tr>
<td>Nipradilol</td>
<td>0.3 mg/kg</td>
<td>5</td>
<td>79.4±6.0*</td>
<td>334.0±14.0</td>
<td>51.2±3.8**</td>
</tr>
<tr>
<td></td>
<td>1.0 mg/kg</td>
<td>6</td>
<td>70.0±2.9</td>
<td>335.0±10.3</td>
<td>28.5±3.4</td>
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<tr>
<td>Hydralazine</td>
<td>0.3 mg/kg</td>
<td>5</td>
<td>75.4±8.1</td>
<td>339.6±11.4</td>
<td>30.6±4.7</td>
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<tr>
<td>Propranolol</td>
<td>1.0 mg/kg</td>
<td>5</td>
<td>66.4±4.1</td>
<td>326.0±8.2</td>
<td>23.8±2.4</td>
</tr>
</tbody>
</table>

Mean±S.E.M.; *P<0.05, **P<0.01.

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**Fig. 2. Effects of nipradilol on MABP, CO, TPR and HR in the pithed rat pretreated with DHE.**

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**Table 2. Initial values of MABP, HR, CO and TPR before administration of saline (control), nipradilol, hydralazine and propranolol in DHE-pretreated pithed rats**

<table>
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<tr>
<th>Group</th>
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Mean±S.E.M.; *P<0.05, **P<0.01.
induced by DHE: DHE (0.1 mg/kg) produced a simultaneous and sustained rise in CVP as well as in MABP (Fig. 4). Increases in CVP and MABP 3 min after DHE administration were 0.55±0.13 mmHg and 28.3±4.4 mmHg (n=3), respectively. When nipradilol (1.0 mg/kg) was injected 3 min after DHE treatment, CVP and MABP were decreased simultaneously by 0.43±0.07 mmHg and 17.7±2.7 mmHg (n=3), respectively. Nipradilol completely abolished the rise in CVP induced by DHE.

Discussion

The present studies demonstrated the venodilating action of nipradilol and also confirmed the cardiovascular effects of DHE which were previously reported by de Metz and van Zwieten (3). DHE produced a simultaneous rise in BP and CO without appreciable changes in TPR and HR in the pithed rat. An increase in CVP with DHE was also observed. DHE is a selective venoconstrictive agent in vivo and in vitro (4, 5). Therefore, it is considered that DHE reduces venous capacity through venoconstriction and increases cardiac filling pressure as blood is translocated from the peripheral to the cardiopulmonary circulation.

Using the DHE treated pithed rat, we compared the effects of nipradilol with those of propranolol and hydralazine. Nipradilol caused a fall in BP and CO, while TPR was unchanged. Nipradilol also reduced CVP.
without any cardiac stimulation. These results indicate that nipradilol dilates venous capacitance vessels and thereby decreases cardiac filling pressure. In contrast, hydralazine dilates preferentially resistance vessels because it reduced BP and TPR without changes in CO. Propranolol produced a transient decrease in BP and TPR. This action is probably due to its membrane stabilizing (6) or calcium entry blocking (7) action in a high dose. Although propranolol caused a certain degree of reduction in HR, there was no significant change in CO, therefore, it seems unlikely that the small reduction of HR would contribute to the decrease in CO in the pithed rat.

Beta-adrenoceptor blocking agents cause a rise in left ventricular end-diastolic pressure through negative chronotropic and inotropic actions. Although nipradilol has a potent β-adrenoceptor blocking action (1), it reduces left ventricular end-diastolic pressure in anesthetized dogs (8). It is likely that the venodilating action of nipradilol compensates for the increase in left ventricular end-diastolic pressure caused by its β-adrenoceptor blocking action as a decrease in CVP with nipradilol was observed in the present study.

Nipradilol decreases TPR as well as CO, BP and HR in anesthetized dogs (8). These findings indicate that nipradilol dilates resistance vessels and the decrease in CO is probably due to both β-adrenoceptor blocking and venodilating actions of nipradilol. The TPR-lowering effect of nipradilol was not observed in the pithed rat because central sympathetic activity is eliminated in this preparation, and arterial vascular resistance is very low. From the present results, although nipradilol dilates veins as well as arteries, it is not clearly determined that the venodilatation induced by nipradilol is mainly responsible for its acute hypotensive effect in intact animals. The dilatation of veins might be important in decreasing BP of animals with high venous tone.

Although more studies are needed to unequivocally link the venodilating action of nipradilol to its antihypertensive effect, our findings suggest such a relationship. In this regard, Nakamura et al. have demonstrated that prolonged administration of nipradilol but not propranolol lessens the reduction in venous distensibility seen in spontaneously hypertensive rats (SHR) (9). It has been reported that venous compliance is decreased and venous contractility is enhanced in human essential hypertension (10–12) and also in experimental hypertensive animals (13–16). A reduction in venous capacity, which would increase cardiac filling pressure and, in turn, elevate cardiac output, has been implicated as an early step in the development of several forms of hypertension (17). It has been also suggested that a transient increase in intrathoracic blood volume due to an inadequate sodium excretion by abnormal kidneys causes a release of Na,K-ATPase in to the circulation and that this inhibitor raises the tone and vascular reactivity of the smooth muscle of the arteries and veins (18). Thus, venoconstriction appears to be an important feature of hypertension. Based on these previous findings, the present results suggest that the venodilating action of nipradilol may be partially involved in the antihypertensive effect obtained in SHR treated chronically with nipradilol (2, 9) and may be of value in treating hypertensive patients.

References


