ANTIHYPERTENSIVE EFFECTS OF NIFEDIPINE ON CONSCIOUS NORMOTENSIVE AND HYPERTENSIVE RATS

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Hypotensive actions of single and repeated administrations of nifedipine were evaluated in comparison with hydralazine in normotensive, spontaneously hypertensive and renal hypertensive rats. Substantial and prolonged falls in blood pressure were observed following oral dosing with 3 mg/kg of nifedipine in renal hypertensive rats, with 10 mg/kg of nifedipine in normotensive and spontaneously hypertensive rats and with 10 mg/kg of hydralazine in all three groups of animals. The hypotensive effect of nifedipine was greater in both forms of hypertensive rats than the normotensive rats, while there was no difference in the hypotensive effect of hydralazine in normotensive and hypertensive animals. In spontaneously hypertensive rats tolerance to nifedipine and hydralazine was not observed with oral administrations for 4 weeks at a daily dose of 10 mg/kg. An increase in heart rate always accompanied the hypotension induced by both drugs, but this tachycardia was seen to a lesser extent with nifedipine than with hydralazine. The mechanism of the selective action of nifedipine in hypertensive rats in contrast to normotensive rats is discussed.

Keywords—nifedipine; hydralazine; hypertensive rats; normotensive rats; anti-hypertensive effect

Nifedipine is a potent Ca\(^{2+}\) antagonistic agent which restricts the transmembrane Ca-influx during excitation.\(^5\) Not only the coronary arteries but also peripheral vessels are dilated by this substance\(^3\) and a decreased peripheral vascular resistance occurs.\(^3\) Thus, nifedipine may be effective for the treatment of arterial hypertension. In fact, antihypertensive effects of nifedipine in patients with hypertension have been studied by several groups of investigators.\(^4\)\(^-\)\(^6\) However, little information is available concerning the effect of this compound on experimentally hypertensive animals.\(^9\),\(^10\)

The purpose of this paper is to describe the antihypertensive effect of nifedipine in normotensive, spontaneously hypertensive and renal hypertensive rats in comparison with hydralazine.

MATERIAL AND METHODS

Acute Experiments — Acute experiments were carried out on male 10 to 12-week-old normoten-

sive, 18 to 25-week-old spontaneously hypertensive (Okamoto and Aoki Strain) and 10 to 12-week-old renal hypertensive rats. The rats were housed under identical conditions and fed standard food and water \textit{ad libitum}.

To prepare renal hypertensive rats, a silver clip was placed on the left renal artery in 5-week-old Wistar rats under pentobarbitone anesthesia. The right kidney was left intact.

On the morning of experiments, rats were anesthetized with ether and a femoral artery was cannulated to measure arterial blood pressure by using a Toyo Meas. pressure transducer (MPU-0.5-290). Electrically integrated values of mean arterial pressure were recorded. Heart rate was determined at intervals by counting the pulse from the blood pressure recordings. Experiments were started 3hr after surgery, at which time the animals had fully recovered from the ether anesthesia.

Chronic Experiments — Male spontaneously
hypertensive rats were orally given nifedipine (10 mg/kg/day), hydralazine (10 mg/kg/day) or water (5 ml/kg/day) for 28 days beginning the age of 22 weeks. Each group included 12 rats. Right before and at 1 hr after the drug administration twice a week, systolic blood pressure and heart rate were measured in the conscious rats by an indirect tail-cuff methods, using a programmed electro-sphygmomanometer (PE-300, Narco Bio-Systems, INC.). Prior to the measurement, rats were placed under conditions of 38° for 10 min.11)

Drugs were dissolved in water and administered orally in a volume of 0.5 ml/100 g body weight.

Drugs used were nifedipine (Sepamit®, Kanebo Ltd., Japan) and hydralazine hydrochloride (Tokyo Kasei Ltd., Japan). Nifedipine was dissolved just before the administration.

Data were reported as mean ± standard errors. Levels of significance were determined by Student's t-test, paired when comparing drug-treated and vehicle-treated animals, and unpaired when comparing hypertensive and normotensive rats. At p-values below 0.05 the difference was considered as significance.

RESULT

Effects of a Single Oral Administration of Nifedipine and Hydralazine on Mean Blood Pressure and Heart Rate in Normotensive and Experimentally Hypertensive Rats

Oral administration of nifedipine caused dose-dependent falls in mean blood pressure in normotensive (Fig. 1), spontaneously hypertensive (Fig. 2) and renal hypertensive (Fig. 3) rats. The peak effect was reached within 15 min. The duration depended on the dose and was over 6 hr at the dose of 10 mg/kg in normotensive and both forms of hypertensive rats. Hydralazine administered orally also lowered blood pressure in

FIG. 1. Effects of Nifedipine and Hydralazine on Blood Pressure (BP, upper) and Heart Rate (HR, lower) in Normotensive Rats

Drugs were given orally. Each value represents the mean ± S.E. of 5 rats.

* Statistically significant p < 0.05 against respective control values.
a dose-dependent manner in these three groups of rats (Fig. 1-3). The hypotensive action of hydralazine was gradual, namely, the maximum response was reached after 30 to 60 min and the duration of action was longer.

Both nifedipine and hydralazine produced a dose-related increase in heart rate in these normotensive and hypertensive animals (Fig. 1-3). In spontaneously hypertensive rats 15 and 30 min after treatment, an increase in heart rate after hydralazine (3 mg/kg) dosing was the same as that after nifedipine (3 mg/kg) dosing, despite the significantly smaller fall in blood pressure with hydralazine (p < 0.05). Similar results were also observed in renal hypertensive rats 15 and 120 min after treatment.

The maximum decrease in the blood pressure after nifedipine dosing was significantly greater in spontaneously and renal hypertensive rats than in normotensive ones, while hydralazine produced almost the same hypotensive effect in these three groups of animals (Fig. 4).

**Effects of Repeated Oral Administration of Nifedipine and Hydralazine on Systolic Blood Pressure and Heart Rate in Spontaneously Hypertensive Rats**

Fig. 5 shows the results obtained in spontaneously hypertensive rats treated orally with vehicle (5 ml/kg/day), nifedipine (10 mg/kg/day) and hydralazine (10 mg/kg/day). In vehicle-treated control animals, the systolic blood pressure before treatment was maintained at almost the same levels (213-221 mmHg) during the observation periods of 4 weeks. There were little changes in the blood pressure and heart rate after the vehicle administration.

The blood pressure and heart rate before the nifedipine administration were pretty much the same as in the control group throughout the observation periods. One hour after nifedipine administration blood pressure fell by 73-99 mmHg. However, there was no significant difference in the degree of the hypotension during 3 to 28 days of nifedipine treatment, compared with 87 ± 5 mmHg on the starting day of

**FIG. 2. Effects of Nifedipine and Hydralazine on Blood Pressure (BP, upper) and Heart Rate (HR, lower) in Spontaneously Hypertensive Rats**

*Drugs were given orally. Each value represents the mean ± S.E. of 5 rats.*

*Statistically significant p < 0.05 against respective control values.*
Antihypertensive Effects of Nifedipine

FIG. 3. Effects of Nifedipine and Hydralazine on Blood Pressure (BP, upper) and Heart Rate (HR, lower) in Renal Hypertensive Rats

Drugs were given orally. Each value represents the mean ± S.E. of 5 rats.

* Statistically significant p < 0.05 against respective control values.

FIG. 4. Effects of Nifedipine and Hydralazine on Blood Pressure (BP) in Normotensive (NR), Spontaneously Hypertensive (SHR) and Renal Hypertensive (RHR) Rats

Maximum percent decrease of respective initial value is indicated. Each column indicates mean value, and vertical line indicates S.E. (n = 5).

**, *** Statistically significant p < 0.01, p < 0.001, respectively, against normotensive rats.
FIG. 5. Effects of Chronic Oral Nifedipine (10 mg/kg/day), Hydralazine (10 mg/kg/day) and Water (5 ml/kg/day) Administration on Systolic Blood Pressure (BP, upper) and Heart Rate (HR, lower) in Spontaneously Hypertensive Rats

Blood pressure and heart rate were measured just before and 1 hr after drug administration. Each value represents the mean ± S.E. of 12 animals.

treatment. Heart rate increased by 50–100 beats/min.

In the hydralazine-treated group, the pre-drug levels of blood pressure during the 3rd to 28th days of treatment were significantly lower \((p < 0.001)\) and the heart rates were significantly higher \((p < 0.01)\) compared with the respective control values. Oral administration of hydralazine produced further fall in blood pressure to a constant level of 100–117 mmHg throughout the entire period of experiment. Heart rate after treatment also increased to the plateau levels of 484 to 508 beats/min. Body weights in animals treated with vehicle, nifedipine and hydralazine were, respectively, 332 ± 2, 335 ± 3 and 336 ± 3 g on the first day of treatment and 336 ± 3, 339 ± 3 and 340 ± 3 g on the 28th day of treatment.

DISCUSSION

Altered calcium availability via membrane has been reported in experimentally hypertensive animals. Hinke (1966) suggested that the vascular smooth muscle cell membrane is more permeable to calcium in animals with hypertension induced by prolonged treatment with desoxycorticosterone. Similar increase in membrane permeability to calcium were also observed in spontaneously hypertensive and renal hypertensive rats. In addition, it has been shown that calcium contents of cardiovascular tissue increase in spontaneously hypertensive and renal hypertensive rats. Thus, it may be valuable to compare the hypotensive effect of nifedipine, calcium antagonist, between normotensive and hypertensive rats.
In the present study, substantial and prolonged falls in blood pressure followed oral dosing with 3 mg/kg of nifedipine in renal hypertensive rats and with 10 mg/kg in spontaneously hypertensive and normotensive rats. The hypotensive effect of nifedipine was greater in spontaneously and renal hypertensive rats than in normotensive ones. This may be due to cure of the abnormal calcium availability in the vasculature of hypertensive rats.

Another possible additional mechanism of the selective hypotensive action of nifedipine on hypertensive animals is the inhibitory action of nifedipine on pressor response to noradrenaline. Nifedipine given in a dose of 0.3 mg/kg i.v. to normotensive rats abolished the pressor response to noradrenaline (1 μg/kg i.v.) but the same dose of hydralazine reduced it significantly but only slightly, although the dose of both drugs produced a similar degree of hypotension (unpublished observation). A recent study\(^{16}\) has demonstrated that pressor reactivity to noradrenaline is greater in spontaneously hypertensive and renal hypertensive rats than in normotensive controls and the hyperresponsiveness to noradrenaline may play an important role in the maintenance of hypertension in the two types of rats. It can be, therefore, expected that nifedipine induces a more pronounced hypotension in these hypertensive rats than in normotensive ones by inhibiting the pressor effect of noradrenaline, a physiological vasoconstrictor.

Hydralazine exerts its hypotensive action mainly by a direct action on smooth arterial muscle.\(^{17,18}\) In the present experiments, this drug produced a more prolonged hypotension than did nifedipine. However, in contrast to nifedipine, hydralazine induced a similar degree of hypotension in both normotensive and hypertensive rats. This may indicate that the mechanism of hypotensive action of hydralazine is different from that of nifedipine. In fact, no information is available concerning a calcium antagonistic effect of hydralazine on vascular smooth muscle.

Tolerance to nifedipine did not develop in spontaneously hypertensive rats during the 28 days of treatment. Hydralazine also produced no tolerance, and this is in general agreement with the results described by Baldoli \textit{et al.} (1973)\(^{19}\) who used renal hypertensive rats. Furthermore, edema formation, which has been observed with many vasodilators,\(^{20}\) did not occur, since there was no effect on body weight in animals after repeated dosing with nifedipine and hydralazine.

Simultaneously with falls in the blood pressure, increases in the heart rate occurred after single and repeated administration of nifedipine and hydralazine in normotensive and hypertensive rats, which may be the consequence of enhanced peripheral sympathetic activity. In both forms of hypertensive rats the tachycardiac action was more pronounced with hydralazine than nifedipine.

In conclusion, nifedipine may be a useful anti-hypertensive agent, because of its selective effects on hypertensive rats.

REFERENCES


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