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Effects of nifedipine on renal responses to several diuretic agents in rats

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Abstract—The influence of the dihydropyridine calcium antagonist nifedipine has been studied on the diuretic response to frusemide, acetazolamide and hydrochlorothiazide in water-loaded (25 mL kg^{-1}) conscious rats. Oral administration of nifedipine (10 mg kg^{-1}) markedly inhibited frusemide- and hydrochlorothiazide-induced diuresis as evidenced by a reduction in 5 h urine volume and urinary sodium and potassium elimination. However, it neither significantly enhanced nor limited urine and electrolyte excretion promoted by acetazolamide. Nifedipine, 5 and 10 mg kg^{-1} but not 1 mg kg^{-1}, significantly ($P < 0.05$) inhibited the diuretic response of hydrochlorothiazide. At doses which affect hydrochlorothiazide diuresis (5 and 10 mg kg^{-1}), nifedipine was found to depress the mean arterial pressure by 32% in normotensive rats. These results are of interest in view of the often reported clinical side effect of nifedipine in promoting peripheral oedema in hypertensive patients and its use in combination with a thiazide or loop diuretic.

The antihypertensive efficacy of the slow calcium channel blocker nifedipine has been well documented in recent years (MacGregor et al 1982, 1983; Schnapp et al 1987). Controlled clinical studies have shown that nifedipine is well suited for use by itself as well as in combination with β-adrenoceptor blockers or diuretics (Duffy & MacDonald 1987). Its usefulness in combination with diuretics, however, is not very clear. Clinical experience suggests that in some patients at least, a diuretic can cause a further decrease in blood pressure when added to a nifedipine therapy (Robinson 1985) while in others no such additive effect was observed (Rosenthal 1982). Acute administration of nifedipine to normotensive and hypertensive subjects produces increased renal blood flow (Yokoyama & Kaburagi 1983), natriuresis and diuresis (Leonetti et al 1982; Schnapp 1989), but the mechanisms of nifedipine-induced natriuresis are incompletely understood and do not show any relationship to fall in systemic blood pressure (Schnapp 1989). Short or long term use of nifedipine is associated with a moderate increase in plasma renin activity and will also promote the development of peripheral oedema which is sometimes severe and resistant to diuretic therapy (Aoki et al 1978; Guazzi et al 1983; Duffy & MacDonald 1987). Experimental studies showed nifedipine to cause overt urine and electrolyte retention in saline-loaded rats (Barret et al 1988). A similar observation has been made by Rao et al (1988) in water-loaded normotensive rats. Since a combination of nifedipine and diuretics is sometimes preferred clinically for the treatment of hypertension, it was of interest to study the effects of nifedipine on systemic blood pressure and on diuretic responses to frusemide, acetazolamide and hydrochlorothiazide in water-loaded, conscious rats.

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Materials and methods

Animals

Wistar female rats, 200–350 g, were maintained under a 12/12 h light/dark cycle at 23 ± 1 °C with free access to a standard pellet diet (Purina rat chow) and water. All experiments were performed between 0900 and 1400 h.

Diuresis in rats

Rats were deprived of food and water for 16 h and received a priming dose of 0·9% NaCl (saline) (25 mL kg^{-1}) by the oral route. The rats were divided into two groups of 10 in each cage and the test drugs nifedipine (10 mg kg^{-1}), hydrochlorothiazide (10 mg kg^{-1}) and acetazolamide (20 mg kg^{-1}), suspended in distilled water containing 0·5% gum arabic, were administered orally in a volume of 25 mL kg^{-1}; frusemide (2 mg kg^{-1}) was given intraperitoneally. The control animals received the same volume of vehicle. The animals were placed in metabolic cages (2 rats/cage) immediately after administration of the drugs. A pooled 5 h urine sample was obtained from each treatment group. Excreted urine volume, pH, urinary sodium and urinary potassium were measured. In another set of experiments, hydrochlorothiazide-induced diuresis was evaluated at doses of 1, 5 and 10 mg kg^{-1} nifedipine in a time course study.

Blood pressure in rats

Rats were anaesthetized with pentobarbitone sodium (40 mg kg^{-1}, i.p.) and the mean arterial pressure was continuously monitored from the right carotid artery through a Statham transducer. Mean blood pressure changes following intraduodenal application of nifedipine (5 and 10 mg kg^{-1}) were measured. Five animals were used for each dose of nifedipine.

Estimation of pH and urinary electrolytes

Urine pH was measured with a pH blood gas analyser (Instrumentation Laboratory Inc. Type 213) and sodium and potassium were measured by a flame photometer (Instrumentation Laboratory Inc. Type 443).

Statistical analysis

Values were expressed as mean ± s.e.m. Analysis of variance and Student's *t*-test were used to evaluate the results.

Table 1. Effect of nifedipine on 5 h urinary volume, pH, sodium and potassium excretion in hydrated conscious rats treated with frusemide, acetazolamide or hydrochlorothiazide.

Treatment	Urinary volume (mL kg^{-1})	pH	Sodium (mEq kg^{-1})	Potassium (mEq kg^{-1})
Control (water)	14·95 ± 2·01	7·25 ± 0·22	0·18 ± 0·04	0·31 ± 0·04
Nifedipine (10 mg, kg^{-1}, p.o.)	7·13 ± 1·73[a]	7·31 ± 0·21	0·08 ± 0·01	0·13 ± 0·02
Frusemide (2 mg kg^{-1}, i. p.)	37·80 ± 2·15[a]	6·97 ± 0·16	2·43 ± 0·11[a]	0·99 ± 0·10[a]
Nifedipine + frusemide	5·90 ± 0·09[b]	6·77 ± 0·13	0·48 ± 0·09[b]	0·42 ± 0·02[b]
Acetazolamide (20 mg kg^{-1}, p.o.)	37·27 ± 2·30[a]	8·69 ± 0·06	4·07 ± 0·42[a]	2·33 ± 0·03[a]
Nifedipine + acetazolamide	34·96 ± 1·93	8·81 ± 0·11	5·17 ± 0·32	2·46 ± 0·14
Hydrochlorothiazide (10 mg kg^{-1}, p.o.)	34·28 ± 1·49[a]	6·08 ± 0·28[a]	2·80 ± 0·11[a]	1·12 ± 0·14[a]
Nifedipine + hydrochlorothiazide	11·22 ± 1·34[b]	6·01 ± 0·39[a]	0·70 ± 0·09[b]	0·69 ± 0·09

Data are presented as means ± s.e.m. of 6 cages (2 animals per cage). a = 95% confidence limits vs vehicle-treated controls; b = 95% confidence limits vs diuretic treated controls (analysis of variance).

Results

The effects of nifedipine on the diuretic effects of frusemide, hydrochlorothiazide and acetazolamide are shown in Table 1. Nifedipine at 10 mg kg^{-1}, a dose frequently used to block slow calcium channels in animals, significantly ($P < 0·05$) inhibited 5 h urine volume, and sodium and potassium excretion in rats. At the doses chosen, all the three diuretics significantly ($P < 0·05$) promoted diuresis. However, these diuretics in combination with nifedipine produced varied results. The increases in urinary volume, sodium and potassium induced by frusemide and hydrochlorothiazide were significantly inhibited by nifedipine. However, the response to acetazolamide was unaltered. As would be expected, acetazolamide promoted a significant rise in urinary pH.

Fig. 1 shows the time course effect of nifedipine (1, 5 and 10 mg kg^{-1}) on the diuresis promoted by hydrochlorothiazide in water-loaded rats. Nifedipine at 5 and 10 mg kg^{-1} caused a significant ($P < 0·05$) decrease in urinary volume and urinary sodium at all time points (1, 2, 3 and 5 h) of observation while depression in potassium elimination was evident only during the first 2 h. The dose of 1 mg kg^{-1} nifedipine had no influence on hydrochlorothiazide-induced diuresis, natriuresis or kaliuresis.

A significant decrease in mean arterial blood pressure was noted following intraduodenal application of nifedipine. The response of 10 mg kg^{-1} was not significantly different from that of 5 mg kg^{-1}. Nifedipine at 5 mg kg^{-1} decreased the mean blood pressure (mm Hg ± s.e.m.) from 146·8 ± 4·28 to 100·2 ± 3·16 (32% decrease) whereas at a higher dose (10 mg kg^{-1}) it decreased the mean blood pressure to 102·4 ± 4·87 from the control value of 150·4 ± 9·06 (32% decrease). The hypotensive effect of nifedipine ensued within 15 min, reached the peak level in 45 min and showed a tendency to recover but did not recover completely within the 3 h observation period.

Discussion

The effects of nifedipine itself and its antagonism of frusemide- and hydrochlorothiazide-induced diuresis observed in the present study are unexpected in view of reported natriuretic and diuretic effects of nifedipine in hypertensive patients (Ene et al 1984; Landmark 1986; Zanchetti & Leonetti 1987; Schnapp 1989) and in animal experiments (Johns 1984). However, the mechanism of natriuretic effect of nifedipine is not yet well established. Among the possibilities, a direct action on the sodium reabsorptive processes in renal tubules is thought to be responsible for the natriuretic effect (Johns 1984; Zanchetti & Leonetti 1987). Johns (1984) indicated that nifedipine in doses

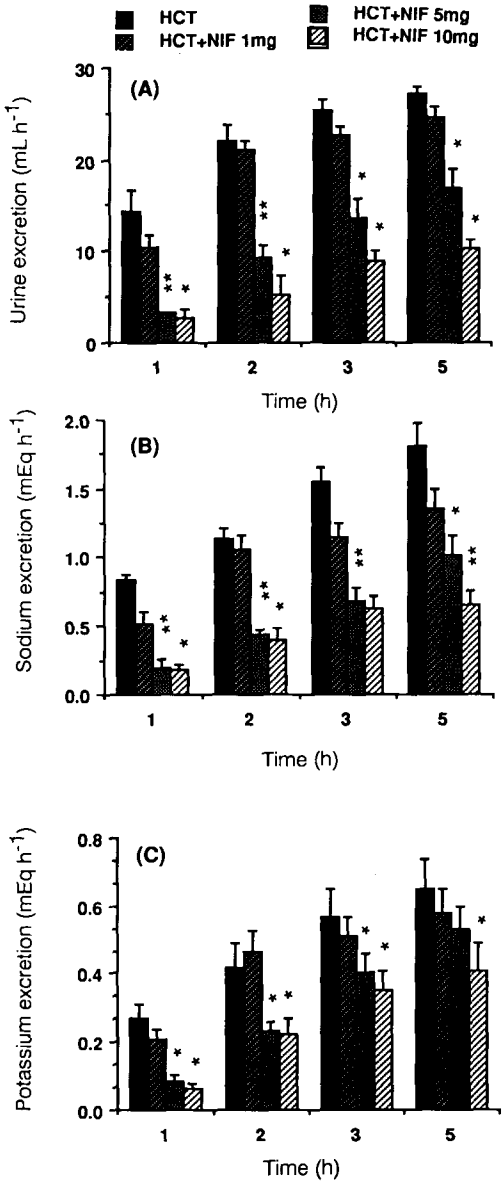

FIG. 1. Effects of nifedipine on hydrochlorothiazide-induced diuresis (A), natriuresis (B) and kaliuresis (C). * $P < 0·05$, ** $P < 0·01$. HCT = hydrochlorothiazide, NIF = nifedipine.

which caused no, or only small, reductions in blood pressure can induce natriuresis in rats whereas at doses that caused moderate reductions in blood pressure, the natriuretic and diuretic effects are not apparent. In the present study, doses of nifedipine (5 and 10 mg kg^{-1}) that inhibit natriuresis and diuresis were able to cause a 32% reduction in systemic blood pressure, indicating a probable relationship between the acute blood pressure fall and the acute changes in sodium excretion, and that nifedipine at high doses may inhibit sodium excretion by its effects on systemic and renal blood vessels.

The mechanism by which nifedipine inhibits frusemide- and hydrochlorothiazide-induced diuresis is also not clear. Nifedipine did not alter the diuretic response to acetazolamide, a drug that primarily acts by inhibiting the enzyme carbonic anhydrase. From the present observations, it would be difficult to speculate on the mechanisms involved in the renal effects of nifedipine, although inhibition of some renal function cannot be excluded.

Because of the reported side-effects of nifedipine in hypertensive patients, extreme caution is necessary in extrapolating the findings observed in normotensive rats to man. Although the acute effects of drugs are certainly important, these effects may differ from those after chronic administration due to factors such as possible adaptive mechanisms, the involvement of volume factors and tolerance towards drugs. However, these results may very well have some clinical relevance since nifedipine administration seems to increase plasma renin activity and also to promote the development of peripheral oedema which is sometimes severe and resistant to diuretic therapy in hypertensive patients. Therefore, keeping in view the observed renal responses and the reported clinical side effect, caution should be exercised in the use of nifedipine as a sole antihypertensive agent or in conjunction with diuretic drugs.

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