Reversal by the Calcium Antagonist Nisoldipine of Norepinephrine-Induced Reduction of GFR: Evidence for Preferential Antagonism of Preglomerular Vasoconstriction

RODGER LOUTZENHISER, MURRAY EPSTEIN, CHARLES HORTON and PHILLIP SONKE
Nephrology Section, Veterans Administration Medical Center and the Department of Medicine, University of Miami School of Medicine, Miami, Florida
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ABSTRACT
We have demonstrated previously that the organic Ca ++ antagonist diltiazem augments the glomerular filtration rate (GFR) of the isolated perfused rat kidney during norepinephrine (NE)-induced vasoconstriction. These earlier studies, however, did not elucidate the precise mechanism or site of action responsible for this effect. Nisoldipine (NIS) interacts with the same Ca ++ channels as diltiazem but differs in its physicochemical properties, binding characteristics and tissue specificity. We examined, therefore, the effects of NIS using an identical model. Renal perfusate flow and GFR were assessed in the isolated perfused rat kidney under conditions of constant renal perfusion pressure (100 mm Hg). NIS (10^-7 M) completely reversed the NE-induced reduction in GFR but was significantly less effective in augmenting renal perfusate flow. In an additional series of experiments, filtration pressure was estimated during these manipulations by monitoring ureteral pressure during ureteral occlusion (stop-flow pressure). The NE-induced decrease in GFR was accompanied by a reduction in stop-flow pressure, which was abolished by the subsequent administration of NIS. Thus, nisoldipine preferentially attenuated NE-induced constriction of pregglomerular resistance vessels but was less effective in reversing the effects of NE on postglomerular arterioles. These findings indicate that separate postreceptor mechanisms mediate the activation of pre- and postglomerular vessels by NE.

The primary role of cytosolic Ca ++ as the second messenger mediating vascular smooth muscle tone is firmly established. Most, if not all, vasoconstrictor agents activate vascular smooth muscle by modifying cellular Ca ++ handling (for review, see Bolton, 1979). Postreceptor events mediating the increase in intracellular Ca ++ include the activation of either receptor-operated or potential-dependent Ca ++ channels (Godfraind, 1976; Meisher et al., 1981), the release of intracellularly bound Ca ++ (Bohr, 1963; Hinke, 1965; Bevan and Waterson, 1971; Deth and van Bremen, 1977) and alterations in intracellular Ca ++ sequestration (Loutzenhiser and van Bremen, 1983a).

Organic Ca ++ antagonists alter vascular tone by interacting with membrane-associated Ca ++ channels (Bolger et al., 1983; Triggle and Swamy, 1983; Glossman and Ferry, 1983), thereby modulating Ca ++ entry into vascular smooth muscle (Fleckenstein, 1977; Thorens and Haeusler, 1979; van Bremen et al., 1981). Calcium antagonists of the dihydropyridine class are particularly selective with regard to the type of Ca ++ entry pathway they affect (Triggle and Swamy, 1983). Furthermore, unlike verapamil, dihydropyridines do not interfere with the binding of adrenergic agonists to adrenoceptors (Motulsky et al., 1983), nor do they affect the release of intracellularly bound Ca ++ or Ca ++-dependent activation of skinned smooth muscle preparations (Saida and van Bremen, 1983). For these reasons, these agents represent unique tools for the study of postreceptor activation processes.

Previous studies from our laboratory demonstrated that the Ca ++ antagonist diltiazem causes a striking augmentation of GFR without appreciably increasing RPF when administered to the isolated perfused rat kidney during norepinephrine-induced vasoconstriction (Loutzenhiser et al., 1985). The present study was designed to characterize further the effects of Ca ++ entry blockade upon the renal hemodynamic response to norepinephrine. Because nisoldipine, a dihydropyridine, exhibits greater tissue selectivity than diltiazem (Triggle and Swamy, 1983) and binds to Ca ++ channels at a site different from diltiazem (Bolger et al., 1983; Glossman and Ferry, 1983), it was anticipated that studies with this agent would provide further insight into the pharmacological basis of this phenomenon. The results indicate that nisoldipine completely reverses the norepinephrine-induced decreases in GFR, although only partially reversing the effects of norepinephrine on RPF. Evi-

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ABBREVIATIONS: GFR, glomerular filtration rate; RPF, renal perfusate flow; SFP, stop-flow pressure.

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dence is added that the disparate responses of RPF and GFR to nisoldipine are attributable to a preferential antagonism of pregglomerular vasoconstriction.

**Methods**

Male Sprague-Dawley rats weighing 350 to 400 g that had been allowed free access to food and water were used as kidney donors. Extracorporeal perfusion of the right kidney was performed utilizing a modification of procedure of Nishiisutuji-Uwo et al. (1967), which has been described previously in detail (Epstein et al., 1980) and is summarized below. Donor animals were anesthetized with Inactin (100 mg/kg b.wt.; Byk-Gulden, Konstanz, West Germany), and the abdominal cavity was exposed by transverse incision. A small (PE-10) catheter was inserted into the right ureter for the collection of urine. The right renal artery was cannulated in situ by introducing the arterial cannula through the superior mesenteric artery and across the aorta. Perfusion with oxygenated media was initiated during the cannulation procedure. The perfused kidney was excised and placed in the recirculating perfusion apparatus described below.

The perfusion media consisted of a Krebs-Ringer's bicarbonate buffer, containing 5 mM d-glucose, 10 mM sodium acetate, 8 g/dl bovine serum albumin (fraction V; Armour Pharmaceutical Co., Kankakee, IL) and a complement of amino acids as described previously (Epstein et al., 1980). The initial volume of media in the system was 150 ml.

The perfusion apparatus used in the present study has also been described in detail elsewhere (Epstein et al., 1980; Loutzenhiser et al., 1982) and will be summarized briefly. This system was designed to provide oxygenated media at a constant pressure, perfuse flow being set by the renal vasculature. The perfusate enters the renal arterial cannula from a pressurized reservoir. The driving force is provided by a regulated inflow of warm, hydrated 95% O₂-5% CO₂, which exits the reservoir via an adjustable back-pressure type regulator (Model 10BP; Fairchild Industrial Products Co., Winston-Salem, NC). Perfusion pressure was monitored at the level of the renal artery by means of a polyethylene catheter inserted through the renal arterial cannula. As reported previously from this laboratory, this technique avoids spurious estimates of the perfusion pressure than can occur during the administration of vasoactive agents (Loutzenhiser et al., 1982). Renal arterial perfusion pressure was maintained at 100 mm Hg throughout the study by adjusting the regulator placed in the gas outflow line. The venous effluent was allowed to drain freely into a water-jacketed funnel and returned to the pressurized reservoir using a calibrated roller pump (Model 7565; Masterflex, Chicago, IL).

The perfused kidneys were allowed to equilibrate for 20 min, and urine samples were then collected at 10-min intervals. Media samples were obtained at the midpoint of the urine collections. Urine volume was determined gravimetrically. GFR was estimated from the renal clearance of carboxyl [¹⁴C] inulin (NEC-164a; New England Nuclear, Boston, MA). RPF was determined by means of an extracorporeal electromagnetic flow transducer (Model 300A; Carolina Medical Electronics, Inc., King, NC) placed in the circuit immediately proximal to the kidney.

In order to delineate further the site of action of norepinephrine and nisoldipine, a second series of experiments was conducted in which ureteral pressure was monitored during ureteral occlusion (SFP). In these experiments, two initial (10 min) urine collections were obtained. The ureteral cannula was then attached directly to a strain-gauge transducer. SFP was then monitored, and the preparation was allowed to equilibrate for at least 10 min. Because the urine-collecting space and the pressure transducer are a closed system, the ureteral pressure increases rapidly until net urine formation ceases (Malvin et al., 1958). After SFP had stabilized, the norepinephrine infusion was initiated. Ten minutes after the onset of norepinephrine infusion, nisoldipine was administered. After 10 min of nisoldipine treatment, phenolamine was administered to antagonize the actions of norepinephrine.

It was anticipated that changes in SFP would be observed if glomerular filtration pressure (i.e., glomerular capillary hydrostatic pressure minus media onotic pressure) were altered by the experimental manipulations described above. The assumptions underlying this approach are: 1) during ureteral occlusion, urine formation ceases and the pressure gradients within the tubular lumen and collecting space are abolished. Under these conditions, the pressure measured in the ureter is directly proportional to the mean tubular pressure. 2) alterations in tubular pressure measured under stop-flow conditions qualitatively follow changes in glomerular hydrostatic pressure minus media onotic pressure (Heller and Horacek, 1980). It is recognized that SFP measured using this approach is an indirect estimate of glomerular filtration pressure. Despite this caveat, gross alterations in filtration pressure occurring during the experimental manipulations should be reflected as qualitatively similar to changes in SFP.

To avoid the beta adrenergic action of norepinephrine, 10⁻⁴ M or 3 × 10⁻⁵ M propranolol (dl-propranolol HCl; Sigma Chemical Co., St. Louis, MO) was added to the media during the initial 10 min of perfusion. After 40 min of perfusion, norepinephrine (L-arterenal HCl; Sigma) was administered as an initial priming dose sufficient to establish a media concentration of 3 × 10⁻⁷ M, followed by a sustaining dose of 10⁻⁹ mol of norepinephrine/min. Nisoldipine (10⁻⁷ M) was administered as a single bolus after 60 min of perfusion, using a stock solution of 10⁻³ M nisoldipine in polyethylene glycol. The amount of vehicle added (0.01%) was without effect upon the parameters measured. Norepinephrine and nisoldipine were added to the venous return line to permit complete mixing. All experiments involving nisoldipine were conducted using sodium lighting to avoid photo-induced deactivation of the dihydropyridine.

In the presentation of data, mean values are followed by the S.E.M. as an index of dispersion. Data were evaluated utilizing Student's t test. Differences with P < .05 were considered statistically significant.

**Results**

**Effects of norepinephrine on GFR and RPF.** The effects of norepinephrine infusion on GFR are depicted in figure 1. In the control group (n = 18), GFR was relatively stable, although a gradual decline occurred during 90 min of perfusion. The administration of norepinephrine at 40 min (n = 9) resulted in a prompt and marked decrease in GFR (from 0.8 ± 0.1 to 0.2 ± 0.2 ml/min/g, P < .005 compared to before norepinephrine and P < .001 compared to the corresponding time period of the control group). The norepinephrine-induced reduction in GFR was sustained for the entire infusion period. The norepinephrine-induced reduction in GFR was anticipated that changes occurring during the experimental manipulations should be reflected as qualitatively similar to changes in SFP.

![Fig. 1. Effects of norepinephrine and nisoldipine on the GFR of the isolated perfused rat kidney. The upper curve (C) depicts spontaneous changes occurring in 18 unmanipulated kidneys serving as time controls. In the experiments illustrated by the two lower curves, norepinephrine infusion was initiated after 40 min of extracorporeal perfusion. In the group receiving norepinephrine alone (O, n = 9), the norepinephrine-induced decrease in GFR was sustained during the entire infusion period. In the group treated with a single bolus of nisoldipine at 60 min (O, n = 7), GFR increased to base-line levels. Values that were significantly different from those obtained with norepinephrine alone (P < .05).](https://jpet.aspetjournals.org)
was sustained throughout the entire 50 min of norepinephrine infusion.

The effects of norepinephrine infusion on RPF are illustrated in figure 2. In the 18 control kidneys, RPF remained constant (39 ± 1 ml/min/g) during 90 min of perfusion (mean ± S.E. depicted as shaded area in fig. 2). Norepinephrine infusion resulted in a 49% decrease in RPF (from 39 ± 2 to 20 ± 3 ml/min/g), which was sustained during the ensuing 50 min of study.

It should be emphasized that the responses described above were observed after pretreatment with propranolol. Although propranolol alone did not alter GFR or RPF in this setting, preliminary experiments indicate that the vasoconstrictive response of this model to norepinephrine is potentiated by propranolol pretreatment (unpublished observations).

**Effects of nisoldipine on norepinephrine-induced decrease in GFR and RPF.** In an initial series of experiments (five kidneys), cumulative dose-response studies were performed to determine the optimally effective concentration of nisoldipine in this model. The results of these experiments are depicted in figure 3. Norepinephrine infusion decreased renal perfusate flow from 35 ± 1 to 20 ± 1 ml/min/g. The administration of 10⁻⁸ M nisoldipine caused a small increase in RPF (i.e., to 22 ± 1 ml/min/g). Increasing the nisoldipine concentration to 10⁻⁷ M produced a more substantial augmentation of RPF (i.e., to 28 ± 1 ml/min/g), whereas increasing nisoldipine to 10⁻⁶ M produced only a marginal further increase (i.e., to 30 ± 0.2 ml/min/g). In contrast, the administration of phentolamine (10⁻⁶ M) promptly and completely reversed the remaining norepinephrine-induced vasoconstriction. Since the maximal effects of nisoldipine were observed using 10⁻⁷ M, this concentration was utilized in the experimental procedures described below.

The reversal by 10⁻⁷ M nisoldipine of the norepinephrine-induced decrease in GFR is depicted in figure 1. In these experiments, norepinephrine was administered to an additional seven kidneys. The initial decrement in GFR upon initiation of the norepinephrine infusion was identical to that described above. When nisoldipine (10⁻⁷ M) was administered to the norepinephrine-treated kidneys, GFR returned to control levels within 10 min (0.7 ± 0.1 ml/min/g, P < .001 and P > .40 respectively, compared to the corresponding time periods of norepinephrine alone and control). In the subsequent two 10-min periods (70–80 and 80–90 min), GFR decreased but remained elevated compared to norepinephrine treatment alone (P < .025). The reasons for the transient nature of the response of GFR to nisoldipine are unclear. It is possible that the previous ischemia may potentiate time-dependent changes in GFR. In six of the kidneys treated with nisoldipine, 10⁻⁶ M phentolamine was subsequently administered at 90 min. GFR increased further in four of these six studies; mean GFR increased from 0.5 ± 0.1 to 0.6 ± 0.1 ml/min/g.

The effects of nisoldipine on RPF of these same preparations during norepinephrine infusion are depicted in figure 2. The initial reduction in RPF observed upon initiation of norepinephrine infusion in these seven kidneys (from 35 ± 2 to 19 ± 1 ml/min/g) was also similar to that observed in the group treated with nisoldipine alone. In contrast to its effect upon GFR, 10⁻⁷ M nisoldipine caused only a modest (i.e., 32%) increase in RPF (from 19 ± 1 to 25 ± 2 ml/min/g, P < .001) compared to nisoldipine alone. RPF remained significantly lower than the corresponding periods of the controls throughout the 30 min of nisoldipine treatment (P < .001). In six of the seven kidneys treated with nisoldipine, 10⁻⁶ M phentolamine was administered after 90 min. The complete recovery of RPF observed upon the addition of phentolamine at 90 min indicates that full vasodilation was possible under these conditions but was not achieved with nisoldipine treatment alone.

**Effects of nisoldipine pretreatment on GFR and RPF.** The effects of nisoldipine on RPF in the absence of norepinephrine and the effects of pretreatment with nisoldipine on the norepinephrine-induced decrease in RPF are illustrated in figure 4. Nisoldipine (10⁻⁷ M, n = 6) did not alter RPF when administered to kidneys before the administration of norepinephrine (i.e., control kidneys). When norepinephrine infusion was subsequently initiated following 20 min of nisoldipine pretreatment, a similar, albeit modest, degree of inhibition of the norepinephrine-induced decrease in RPF was observed (fig. 4). Thus, regardless of whether nisoldipine had been added before or during norepinephrine administration, the effects on RPF were similar.

The effects of nisoldipine on GFR in the absence of norepi-
Effects of Nisoldipine on Isolated Rat Kidney

The kidneys were allowed to equilibrate for 20 min. This was followed by two 10-min urine collections to assure that the preparations were functionally intact and stable. The GFR values of these seven preparations were 0.8 ± 0.1 and 0.9 ± 0.1 ml/min/g for 20 to 30 min and 30 to 40 min, respectively. At 40 min of perfusion, the ureter was connected to a pressure transducer. Norepinephrine (3 × 10⁻⁷ M), nisoldipine (10⁻⁷ M) and phentolamine (10⁻⁶ M) were then administered sequentially at 10-min intervals. The effects of these agents on RPF and SFP are depicted in figures 6 and 7, respectively.

The changes in RPF occurring during the stop-flow experiments are illustrated in figure 6. After 40 min of perfusion, during which time the ureteral catheter was unobstructed, RPF achieved a value of 31 ± 1 ml/min/g. On connecting the ureteral catheter to the pressure transducer, RPF decreased slowly to 29 ± 1 ml/min/g. Norepinephrine infusion caused a 45% decrease in RPF (i.e., from 29 ± 1 to 16 ± 1 ml/min/g). This norepinephrine-induced reduction in RPF was similar in magnitude to that occurring under free urine flow conditions (i.e., fig. 2). The administration of 10⁻⁷ M nisoldipine caused RPF to increase from 16 ± 1 to 19 ± 1 ml/min/g (P < .05). In contrast to the modest increase in RPF caused by nisoldipine, the administration of phentolamine at 70 min resulted in a

Effects of norepinephrine and nisoldipine on SFP and RPF. In order to determine if the effects of nisoldipine upon GFR were mediated by an elevation in filtration pressure (i.e., via preglomerular vasodilation), RPF and SFP were monitored in an additional group of seven kidneys. In these experiments,

1. Comparison of the effects of nisoldipine on RPF before and during norepinephrine infusion. The lower curve (O, n = 7) depicts data from figure 2 and shows the modest recovery of RPF observed when nisoldipine was administered during norepinephrine infusion. In the upper curve (O, n = 6), nisoldipine was administered as a single bolus after 40 min of perfusion. Whereas nisoldipine had no direct effect on RPF when administered alone, pretreatment with this agent produced an inhibition of the response to norepinephrine similar to that observed when nisoldipine was added during norepinephrine infusion (i.e., when infusion was initiated after 60 min of perfusion).

2. Comparison of the effects of nisoldipine on GFR before and during norepinephrine infusion. The lower curve (O, n = 7) depicts data from figure 1 and shows a norepinephrine-induced decrease in GFR with complete recovery when nisoldipine was administered during norepinephrine infusion. In the upper curve (O, n = 6), nisoldipine was administered as a single bolus after 40 min of perfusion. Nisoldipine did not increase GFR when administered alone, but pretreatment with this agent attenuated the response to norepinephrine infusion initiated 20 min later (at 60 min). *The times at which these two groups differed significantly.

3. Alterations in RPF induced by the administration of norepinephrine, nisoldipine and phentolamine under stop-flow conditions (n = 7). After 40 min of perfusion, the ureteral catheter was connected to a strain-gauge transducer for measurement of SFP. The responses to norepinephrine, nisoldipine and phentolamine under these conditions were similar to those observed during free urine flow (fig. 2).

4. SFP studies in the isolated perfused rat kidney. Ureteral pressure was monitored during the infusion of norepinephrine and during subsequent treatment with nisoldipine and phentolamine (n = 7). Pressure was measured by attaching the ureteral catheter to a strain-gauge transducer after 40 min of perfusion. Norepinephrine infusion resulted in a prompt decrease in SFP that was markedly reversed by nisoldipine. Phentolamine caused an additional, albeit smaller, increase in SFP.
We conclude that the increase in GFR was attributable to
when administered in the absence of norepinephrine (fig. 5),
based on levels (fig. 2). Phentolamine, however, did not in-
crease GFR beyond the control level already attained with
nisoldipine alone. Because nisoldipine did not increase GFR
prompted us to extend these studies to the dihydropyridine
demonstrated
experimental design. Previous studies from this laboratory
is capable of reversing the reductions in GFR induced by the
calcium antagonist nisoldipine.
Furthermore, since the isolated kidney exhibits no intrinsic
response can be assessed under defined
conditions in which the hormonal factors
tone, the vascular response can be assessed under defined
effects of these agents and the resulting compensatory reflexes.
In contrast to the above enumerated in vivo studies, the
isolated perfused rat kidney should constitute a preferred ex-
perimental model for evaluating the renal vascular response to
calcium antagonists. Renal perfusion pressure can be main-
tained constant in this model, thus avoiding the hypotensive
effects of these agents and the resulting compensatory reflexes.
Furthermore, since the isolated kidney exhibits no intrinsic
tone, the vascular response can be assessed under defined
conditions in which the hormonal factors are determined by
experimental design. Previous studies from this laboratory
demonstrated that, during norepinephrine infusion of the
isolated perfused rat kidney, diltiazem increases GFR but not RPF
(Loutzenhiser et al., 1985). Our observations with diltiazem
prompted us to extend these studies to the dihydropyridine
calcium antagonist nisoldipine.
The results of the present study demonstrate that nisoldipine
is capable of reversing the reductions in GFR induced by the
acute administration of norepinephrine. When administered
during norepinephrine-induced vasoconstriction, nisoldipine
carried a marked increase in GFR to control levels, with only a
modest increase in RPF (figs. 1 and 2). The subsequent addition
of phentolamine succeeded in returning RPF to the untreated
base-line levels (fig. 2). Phentolamine, however, did not in-
crease GFR beyond the control level already attained with
nisoldipine alone. Because nisoldipine did not increase GFR
when administered in the absence of norepinephrine (fig. 5),
we conclude that the increase in GFR was attributable to
antagonism of the response to norepinephrine rather than to
an independent augmentation of GFR.
The preferential augmentation of GFR by nisoldipine may
be due to a selective antagonism of norepinephrine-induced
vasoconstriction of the afferent arterioles. Norepinephrine has
been demonstrated to induce an increase in both afferent and
effluent arteriolar resistance (Myers et al., 1975). If nisoldipine
decreases afferent arteriolar resistance in this setting, an
elevation of filtration pressure would promote the observed
increase in GFR. Alternatively, nisoldipine may act on the glo-
merular capillary ultrafiltration coefficient (Kf), as has been
reported to occur with verapamil during angiotensin II admin-
istration (Ichikawa et al., 1979). Our observation that norepi-
ephrine caused a decrease in SFP and that this decrease was
markedly reversed by nisoldipine (fig. 7), however, supports the
formulation that nisoldipine acts on the renal vasculature and
raises GFR by increasing filtration pressure.
The salutary effects of nisoldipine upon GFR are most prob-
ably mediated by modulation of smooth muscle Ca2+ move-
ments. As we have reported previously (Loutzenhiser et al.,
1985), diltiazem causes an identical increase in GFR when
administered to the isolated perfused kidney during norepi-
ephrine-induced vasoconstriction. In accordance with the
present observations with nisoldipine, diltiazem also produced
little effect on RPF. At the doses used, nisoldipine and diltiazem
exert comparable effects upon potential-dependent Ca2+ fluxes
in isolated vascular tissues (Loutzenhiser and van Breemen,
1983b). Verapamil and its congeners also modulate Ca2+
 movements through potential-dependent channels and might there-
fore be expected to produce similar effects. In contrast to
diltiazem and nisoldipine, however, verapamil markedly attenu-
ates the norepinephrine-induced decrease in RPF in addition
to its effects upon GFR (Malis et al., 1983). Even though
differences in selectivity for Ca2+ channels could produce this
divergent effect on RPF, it is also possible that this action is
related to other actions of verapamil. For example, unlike
diltiazem or dihydropyridines, verapamil binds to and displaces
norepinephrine from the alpha adrenoceptor (Motulsky et al.,
1983) and affects other receptor systems (Triggle and Swamy,
1983). Results obtained with verapamil should, therefore, be
interpreted with caution.
Although all calcium antagonists may have actions unrelated
to their effects upon Ca2+ movements, it is unlikely that our
observations with nisoldipine are related to such secondary
properties. Although diltiazem and nisoldipine produced similar
effects upon GFR and RPF, it should be emphasized that these
two agents differ markedly in a number of physicochemical and
pharmacological attributes. In comparison to diltiazem, niso-
dipine is much more lipophilic and has a greater selectivity for
vascular smooth muscle than cardiac tissue (Triggle and Swamy,
1983). Additionally, radioligand binding studies suggest that
the binding site at which dihydropyridines interact with the
Ca2+ channel differs from that occupied by diltiazem (Bob-
ner et al., 1983; Glossman and Ferry, 1983). Finally, unlike
diltiazem, nisoldipine has no effect upon the release of intra-
cellular Ca2+ stores and has no inhibitory effect on calmodulin
(Saida and van Breemen, 1983). Because nisoldipine and dilti-
azem differ in the above delineated aspects but share the ability
to modulate Ca2+ influx, a logical interpretation of these studies
is that the preferential afferent vasoconstriction by these two agents
is due to this common pharmacological property.
The differential responses of GFR and RPF to calcium
antagonists may relate to differing mechanisms of activation of afferent and efferent arterioles. During different modes of stimulation, Ca$^{2+}$ may enter through Ca$^{2+}$ channels differing in their sensitivity to organic calcium antagonists. Depolarization-induced contractions are mediated by potential-dependent Ca$^{2+}$ channels that are the primary site of action of the dihydropyridine class of calcium antagonists. Norepinephrine constricts rabbit ear artery (Droogmens and Casteels, 1977), and pulmonary artery (Su et al., 1964; Somlyo and Somlyo, 1968) by activating Ca$^{2+}$ entry pathway that is not dependent upon membrane depolarization. On the other hand, norepinephrine-induced contractions of rabbit basilar artery are closely coupled to membrane depolarization (Harder et al., 1981) and exhibit a greater sensitivity to Ca$^{2+}$ antagonists than those of rabbit ear artery (McCalden and Bevan, 1981; Bevan, 1983). Furthermore, there is evidence that norepinephrine may activate receptor-operated Ca$^{2+}$ channels in rat mesenteric resistance vessels that are more sensitive to calcium antagonists than the potential-dependent channels activated by KCl (Cauvin et al., 1984). It is apparent, therefore, that the mechanisms whereby norepinephrine stimulates Ca$^{2+}$ entry may vary in different vascular beds. Accordingly, afferent and efferent arterioles may differ in the degree of norepinephrine-induced depolarization mediating the response, the types of receptor-operated channels or the dependency of the contractile response upon Ca$^{2+}$ influx. The current observations suggest that nisoldipine preferentially affects those processes mediating the afferent arteriolar response to norepinephrine.

In conclusion, we have demonstrated that nisoldipine is capable of markedly reversing norepinephrine-induced decreases in GFR. The available evidence suggests that this action is due to a selective vasodilation at the level of the afferent arteriole. The renal vasculature thus appears to exhibit heterogeneity in regard to the postreceptor mechanism of norepinephrine-induced vasoconstriction. It remains to be determined, however, if the preferential effect of nisoldipine upon the afferent responses to alpha adrenergic stimulation that we observe in this in vitro model also occurs in vivo. Regardless, the present observations warrant further studies to assess the applicability of such agents in a wide array of clinical disorders characterized by renal vasoconstriction.

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References

Send reprint requests to: Rodger Loutzenhiser, Ph.D., Nephrology Section (111C1), Veterans Administration Medical Center, 1201 N.W. 16th St., Miami, FL 33125.