Selective Antagonism of Humoral Versus Neural Vasoconstrictor Responses by Nisoldipine

RODNEY W. LAPPE, KIRK W. BARRON, JAMES E. FABER, AND MICHAEL J. BRODY

SUMMARY The effects of nisoldipine administration on vascular reactivity to humoral and neural vasoconstrictor stimuli were examined in the intact rat. For these experiments, rats were instrumented with miniaturized pulsed Doppler flow probes to allow continuous measurement of renal, mesenteric, and hindquarters blood flow. In conscious and anesthetized rats, intravenous doses of angiotensin II (75 and 150 ng/kg), norepinephrine (0.6 and 1.2 μg/kg), and epinephrine (0.6 and 1.2 μg/kg) caused dose-dependent increases in arterial pressure and renal and mesenteric vascular resistance. Nisoldipine (0.7 μg/min) administration significantly attenuated (p < 0.05) the pressor and regional vasoconstrictor actions of all three circulating pressor agents; however, nisoldipine infusion had little effect on neurally mediated regional vasoconstrictor responses elicited by electrical stimulation of the posterior hypothalamus or greater splanchnic nerve. These data indicate that nisoldipine depressed vascular responsiveness to humoral vasoconstrictor agents, while neural vasoconstrictor responses were unaffected. Thus nisoldipine appears to exert preferential antagonistic effects on humoral rather than on neural vasoconstrictor stimuli. (Hypertension 7: 216-222, 1985)

KEY WORDS • calcium entry blockers • norepinephrine • epinephrine • angiotensin II • neural vasoconstriction • vascular reactivity • regional vascular resistance

THE second-generation dihydropyridine calcium entry blocker (CEB) nisoldipine has been demonstrated to lower total peripheral resistance in experimental animals and hypertensive patients. Several investigators have suggested that, in addition to direct smooth muscle relaxation, nisoldipine may lower arterial pressure, in part, by noncompetitively antagonizing α-adrenergic receptor vasoconstrictor responses. Nisoldipine and other CEBs have been reported to selectively antagonize α1-adrenergic receptor mediated vasoconstriction in isolated smooth muscle and in pithed rats and cats. These effects may depend on the specific tissue or animal species being studied, however; other investigators have reported that CEBs attenuate both α1- and α2-adrenergic vasoconstriction. In addition to their effects on α-adrenergic receptor responses, CEBs appear to inhibit angiotensin II (ANG II) vasoconstrictor responses in the isolated perfused hindquarters of the dog and the pithed rat. The effects of CEBs on vascular reactivity to pressor stimuli in intact animals, however, are relatively unknown.

In a previous study in our laboratory, using a pulsed Doppler flowmeter to monitor regional blood flow, we described the effects of nisoldipine on arterial pressure and regional vascular resistance. Nisoldipine was found to reduce arterial pressure and vascular resistance in a dose-dependent manner; however, the mechanism behind these actions was not investigated. The purpose of the present study was to examine the nature of the hypotensive effect of nisoldipine. Specifically, we sought to (1) examine the effects of nisoldipine on regional vascular reactivity to ANG II, norepinephrine, and epinephrine in anesthetized and conscious rats and (2) compare the effects of nisoldipine on the vasoconstrictor actions of circulating and neurally released norepinephrine in the anesthetized rat.

Methods

Posterior Hypothalamic Stimulating Electrode
Electrical stimulation of the posterior hypothalamus area of the rat brain was used to elicit neurally mediated pressor responses in the rat. For these studies, male
Sprague-Dawley rats were anesthetized with ketamine/acepromazine (0.1 ml/kg), in a solution of ketamine (100 mg/ml) and acepromazine (10 mg/ml), and placed in a Kopf small animal stereotaxic unit. A bipolar electrode (MS 303/2, Plastic Products, Roanoke, VA) was stereotaxically positioned in the brain 4.0 mm posterior to the bregma, 0.35 mm lateral to the midline, and 7.0 mm ventral to the surface of the brain. The electrode was cemented to the skull with jeweler’s screws and dental cement. Rats received an intramuscular injection of penicillin (250,000 U) and were allowed to recover for 4 to 6 days before undergoing further operations.

Experiments in Anesthetized Rats

Rats (250–350 gm) previously implanted with posterior hypothalamic electrodes were anesthetized with Dial (allobarbital)-urethane (0.65 ml/kg, i.p.) and placed on a heated surgical board. A cannula (PE-10) was inserted in the femoral artery to allow measurement of arterial pressure. Two cannulas (PE-10) were placed in the femoral vein to facilitate the infusion of nisoldipine and bolus injections of pressor agents. Miniaturized pulsed Doppler flow probes were carefully positioned on the left renal artery, superior mesenteric artery, and abdominal aorta to allow measurement of blood flow in the renal, mesenteric, and hindquarters vascular beds. In one group of rats (n = 9) an acute bilateral adrenalectomy was performed to eliminate the release of adrenal catecholamines during posterior hypothalamic stimulation. In a second group of rats (n = 6), the adrenal glands were left intact and the greater splanchnic nerve was dissected free of connective tissue and placed across a bipolar platinum electrode. The nerve was then crushed proximal to the electrode. Rats were allowed to stabilize for 40 minutes.

To examine the effects of nisoldipine on humoral vasoconstrictor responses, bolus injections of norepinephrine (0.6 and 1.2 µg/kg), epinephrine (0.6 and 1.2 µg/kg), and ANG II (75 and 150 ng/kg) were administered intravenously before and during the infusion of nisoldipine (0.7 µg/min). Similarly, neural pressor responses, elicited by frequency-graded electrical stimulation (Grass S44 Stimulator, Quincy, MA, USA) of the posterior hypothalamus (14 V, 0.5 msec duration, 10–6 Hz) or greater splanchnic nerve (14 V, 0.5 msec duration, 2–16 Hz) were examined before and during nisoldipine infusion.

Experiments in Conscious Rats

Rats were instrumented with miniaturized pulsed Doppler flow probes to record blood flow in the renal, mesenteric, and hindquarter vascular beds. The surgical procedure has been described in detail. In brief, rats were anesthetized with pentobarbital (50 mg/kg) and atropine (0.5 mg/kg, i.p.). Through a midline incision, the flow probes were positioned around the left renal artery, superior mesenteric artery, and the abdominal aorta. The wire leads were tunneled subcutaneously and exteriorized at the base of the skull. The wires were soldered to a small receptacle cemented to the skull with dental acrylic cement. Cannulas were inserted in the femoral artery and vein to facilitate measurement of arterial pressure and delivery of drugs. The cannulas were tunnelled subcutaneously and exteriorized at the base of the skull. Cannulas were filled with heparinized saline (50 µg/ml) and were sealed when not in use. Rats received penicillin (250,000 U) and were allowed to recover for approximately 1 week.

All experiments were performed on conscious, freely moving rats in their home-cage environment. On the day of the experiment, hemodynamic responses to intravenous doses of norepinephrine, epinephrine, and ANG II were recorded. Nisoldipine was administered as a bolus injection (100 µg/kg), and pressor challenges were repeated. Rats received a 50 µg/kg supplemental dose of nisoldipine every 30 minutes to maintain the hypotensive efficacy of the CEB.

Data Analysis

Maximal responses to interventions are expressed as changes in pressure or resistance as a percentage of baseline values in these parameters. Resistance for a given bed is calculated as mean arterial pressure/Doppler shift (mm Hg/kHz). Because percentage changes in Doppler shift (blood velocity) that are obtained with the Doppler flow probe have been shown to be directly and linearly related to true percentage changes in volume flow,78 this calculation is a valid method for determining percentage changes in regional vascular resistance. Data are presented as mean changes from baseline ± SEM. Prenisoldipine and postnisoldipine responses were compared statistically with Student/Neuman-Kuels multiple treatment comparison or an analysis of variance (ANOVA) with p < 0.05 designated as the probability value for statistical significance. A Student-Neuman test was used to compare individual points after ANOVA.

Results

Nisoldipine, whether infused or administered as a bolus, had pronounced hypotensive actions in both anesthetized and conscious rats. Both groups of rats had similar mean arterial pressures during the prenisoldipine control period (Table 1). Nisoldipine administration significantly reduced arterial pressure and hindquarters and mesenteric vascular resistance in both groups. Renal vascular resistance was not significantly altered by nisoldipine administration.

Vascular Reactivity

Humoral Vasoconstriction

In addition to lowering arterial pressure, nisoldipine administration exhibited marked effects on vascular reactivity to circulating pressor agents in anesthetized rats (Figures 1–3). Before nisoldipine infusion administration of ANG II increased arterial pressure (Figure 1) and appreciably elevated renal and mesenteric vascular resistance. Hindquarters responses to ANG II were somewhat variable, probably because of reflex
TABLE 1. Effects of Nisoldipine Administration on Baseline Hemodynamic Parameters in Anesthetized and Conscious Rats

<table>
<thead>
<tr>
<th>Group</th>
<th>MAP</th>
<th>%Δ Regional vascular resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Anesthetized rats (n = 24)</td>
<td>107±2</td>
<td>76±2*</td>
</tr>
<tr>
<td>Conscious rats (n = 10)</td>
<td>112±2</td>
<td>76±3*</td>
</tr>
</tbody>
</table>

*%Δ = change in resistance after nisoldipine administration as a percentage of baseline resistance before nisoldipine administration.

MAP = mean arterial pressure; Pre = pre-nisoldipine values; Post = post-nisoldipine values.

FIGURE 1. Effects of nisoldipine administration on the hemodynamic responses to intravenous bolus injections of ANG II in the anesthetized rat. Nisoldipine administration significantly attenuated the pressor, renal, and mesenteric vasoconstrictor responses to norepinephrine. %Δ = change in mean arterial pressure; Vas. Resist. = vascular resistance; HQ = hindquarter; %Δ = percent change; * = p < 0.05, comparison of pre-nisoldipine responses with post-nisoldipine responses.

FIGURE 2. Effects of nisoldipine administration on the hemodynamic responses to circulating norepinephrine in the anesthetized rat. The pressor, renal, and mesenteric vasoconstrictor effects of norepinephrine were significantly suppressed by nisoldipine infusion. %Δ = change in mean arterial pressure; Vas. Resist. = vascular resistance; HQ = hindquarter; %Δ = percent change; * = p < 0.05, comparison of pre-nisoldipine responses with post-nisoldipine responses.

FIGURE 3. Actions of nisoldipine on hemodynamic response to epinephrine in the anesthetized rat. After nisoldipine renal vasoconstrictor responses were converted to renal vasodilation, during nisoldipine infusion, the pressor actions of ANG II were attenuated and the ANG II-induced renal and mesenteric vasoconstrictor responses were significantly decreased (p < 0.05).

Nisoldipine administration also significantly reduced vascular responses to circulating catecholamines (p < 0.05). As illustrated in Figure 2, before nisoldipine infusion administration of norepinephrine caused a dose-dependent increase in mean arterial pressure and renal and mesenteric vascular resistance. Hindquarters resistance was not significantly altered by norepinephrine administration. As with ANG II, administration of nisoldipine attenuated the pressor actions of norepinephrine and the vasoconstrictor responses in the renal and mesenteric vascular beds.

Epinephrine administration also increased arterial pressure and markedly elevated renal and mesenteric vascular resistance. Large decreases in hindquarters vascular resistance, probably due to β-adrenergic receptor stimulation, also were observed with epinephrine.
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TABLE 2. Effects of Nisoldipine Administration on Vascular Reactivity to Vasoconstrictor Agents in Conscious Rats (n = 9)

<table>
<thead>
<tr>
<th>Drug</th>
<th>MAP (Δ mm Hg)</th>
<th>Renal</th>
<th>Hindquarters</th>
<th>Mesenteric</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6 μg/kg</td>
<td>34 ± 3</td>
<td>6 ± 2*</td>
<td>169 ± 38</td>
<td>24 ± 8*</td>
</tr>
<tr>
<td>1.2 μg/kg</td>
<td>42 ± 5</td>
<td>10 ± 2*</td>
<td>283 ± 64</td>
<td>41 ± 10*</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6 μg/kg</td>
<td>22 ± 4</td>
<td>5 ± 3*</td>
<td>71 ± 21</td>
<td>0 ± 4*</td>
</tr>
<tr>
<td>1.2 μg/kg</td>
<td>29 ± 4</td>
<td>6 ± 3*</td>
<td>211 ± 75</td>
<td>0 ± 4*</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>75 ng/kg</td>
<td>28 ± 2</td>
<td>5 ± 2*</td>
<td>347 ± 60</td>
<td>23 ± 7*</td>
</tr>
<tr>
<td>150 ng/kg</td>
<td>30 ± 2</td>
<td>8 ± 1*</td>
<td>346 ± 51</td>
<td>34 ± 5*</td>
</tr>
</tbody>
</table>

*p < 0.05, comparison of prenisoldipine responses with postnisoldipine responses.

MAP = mean arterial pressure, Pre = responses before nisoldipine; Post = responses after nisoldipine; %Δ = percent change in resistance.

Rine administration. After nisoldipine administration the pressor and mesenteric vasoconstrictor actions of epinephrine were significantly attenuated (p < 0.05). Interestingly, after nisoldipine administration, renal vasoconstriction in response to epinephrine was converted to renal vasodilation. Hindquarters vasodilator responses to epinephrine also were significantly reduced (p < 0.05) after nisoldipine administration in the anesthetized rat.

Nisoldipine administration also depressed vascular reactivity in the conscious rat. As summarized in Table 2, the injections of ANG II, norepinephrine, and epinephrine all increased arterial pressure and renal and mesenteric vascular resistance in the conscious rat. As in the anesthetized rat, ANG II and norepinephrine injections had no significant effects on hindquarters vascular resistance, while epinephrine administration elicited hindquarters vasodilation. Nisoldipine administration attenuated the pressor actions of all three circulating pressor agents and markedly depressed renal and mesenteric vasoconstrictor responses.

Neural Vasoconstriction

Stimulation of the posterior hypothalamus in adrenalectomized rats caused a frequency-dependent increase in mean arterial pressure, renal vascular resistance, and mesenteric vascular resistance (Figure 4). Hindquarters vascular resistance was not significantly altered in adrenalectomized rats. During nisoldipine infusion the stimulation-induced increases in arterial pressure were not significantly different from preinfusion responses. Similarly, mesenteric vasoconstrictor responses to posterior hypothalamic stimulation were not affected by nisoldipine administration. The renal vasoconstrictor responses were somewhat less after nisoldipine infusion, but the differences were not statistically significant.

Stimulation of the greater splanchnic nerve caused a frequency-dependent increase in mesenteric vascular resistance (Figure 5). Unlike posterior hypothalamic stimulation, however, mean arterial pressure was not altered during splanchnic nerve stimulation. Vasoconstrictor responses in the mesenteric bed during nisoldipine infusion were not significantly different from preinfusion responses.

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Discussion

One of the goals of this study was to examine the actions of nisoldipine on regional vascular reactivity to endogenous pressor agents in the intact rat. Other investigators have previously demonstrated that CEBs suppressed vascular responsiveness to vasoconstrictor agents in vitro and in ganglion-blocked or pithed animals. 

Our results indicate that nisoldipine attenuates the pressor actions of circulating pressor agents in rats with an intact sympathetic nervous system. Because all the pressor agents tested are endogenous to the rat, a portion of the hypotensive action of nisoldipine and, perhaps, other CEBs may be mediated through antagonism of the pressor actions of several circulating vasoconstrictor hormones, under those conditions (e.g., anesthesia, certain forms of hypertension, stress) when arterial pressure is sustained in part by high circulating levels of these factors.

Nisoldipine has been demonstrated to be a potent displacer of $^3$H-nitrendipine binding in rat aortic membrane preparations, which indicates that nisoldipine interacts with the dihydropyridine binding site at or on the calcium channel. Preliminary data also suggest that nisoldipine may have a slower dissociation rate, which may explain its prolonged duration of action.

In addition, nisoldipine has been demonstrated to be the most potent dihydropyridine in relaxing potassium-depolarized aortic strips, a further indication of its interference with calcium flux. Indeed, all of the cardiovasculard actions of nisoldipine appear to be attributable to its calcium-blocking effects.

There is evidence from many laboratories that the blood pressure of conscious, resting, and unrestrained normotensive rats is not sustained to a significant extent by circulating ANG II, vasopressin, or adrenal catecholamines, but rather is primarily a function of sympathetic vasoconstrictor nerve activity. Because nisoldipine did not have an appreciable effect on neurally evoked vasoconstriction and pressure elevation in the present study, the mechanism responsible for the hypotensive effect of nisoldipine in the conscious animals is not clear. One possibility that could reconcile this inconsistency is that nisoldipine might lower resting sympathetic nerve activity by an effect on the discharge rate of vasomotor neurons within the central nervous system. In preliminary studies, we have observed that administration of nisoldipine into the cerebroventricular system of conscious rats lowers regional vascular resistance and arterial pressure. While these data are consistent with a possible central action of nisoldipine, it was not possible to clearly determine if these actions reflected leakage of nisoldipine across the blood-brain barrier into the systemic circulation. Further studies will be required to address the possibility of a central action of nisoldipine on sympathetic vascular tone.

Nisoldipine was found to be equieffective in both anesthetized and conscious rats. In both groups of rats, vascular reactivity was suppressed. These data suggest that the suppression of regional vascular reactivity by nisoldipine was nonspecific. As both α-adrenergic receptor and ANG II-receptor mediated vasoconstrictor responses were attenuated, nisoldipine did not appear to act as a specific vascular receptor antagonist, at least with respect to responses produced by vasoconstrictors carried in the blood. A more likely possibility is that the effects of nisoldipine were mediated by blocking the influx of extracellular calcium in response to receptor activation.

The vasoconstrictor responses to ANG II may have been due to the direct constrictor actions of ANG II or could reflect indirect facilitatory actions of ANG II on sympathetic nerve transmission. Blockade of the ANG II pressor responses with nisoldipine may, in fact, represent antagonism of a combination of ANG II- and catecholamine-induced vasoconstriction. As nisoldipine had little effect on the vasoconstrictor actions of sympathetic nerve stimulation, the facilitatory actions of ANG II should have remained intact after nisoldipine administration. Because the ANG II responses were markedly attenuated, it is likely that, in the present experiment, the majority of the vasoconstrictor responses observed after bolus injections of ANG II were due to excitation of ANG II vascular receptors.

No regional specificity in suppressing vascular reactivity was observed with nisoldipine administration. Of the three vascular beds examined, renal and mesenteric vasoconstrictor responses were equally attenuated by nisoldipine. Little suppression of hindquarters vascular reactivity was observed after nisoldipine administration; however, no consistent vasoconstrictor responses were observed in the hindquarters before nisoldipine administration. The variability observed in
the hindquarters responses was probably caused by reflex vasodilation, which masked the vasoconstrictor actions of the pressor agents.

Interestingly, in the anesthetized, but not in the conscious, rat, marked renal vasoconstriction in response to epinephrine was converted to renal vasodilation after nisoldipine administration. This phenomenon was not observed with either ANG II or norepinephrine, where small vasoconstrictor responses were still observed after nisoldipine administration. Although the mechanism of this reversal is not yet known, it is possible that blockade of \( \beta \)-adrenergic receptor mediated vasoconstriction by nisoldipine in the kidney may allow for the expression of adrenergic receptor mediated renal vasodilation.

Although epinephrine administration elicited marked hindquarters vasodilation in the anesthetized and the conscious rat, which was significantly reduced by nisoldipine administration, it is unlikely that these findings were the result of a nisoldipine-\( \beta \)-adrenergic receptor interaction. The lack of effectiveness of epinephrine in the hindquarters after nisoldipine administration probably was more attributable to the marked decrease in baseline hindquarters vascular resistance caused by nisoldipine (Table 1).

In light of the antagonistic effects of nisoldipine on vasoconstrictor responses to circulating pressor agents, particularly circulating norepinephrine, it would be expected that nisoldipine might similarly attenuate the pressor and vasoconstrictor actions of neurally released norepinephrine. This was not the case. Neurogenic vasoconstrictor responses, whether elicited by central or peripheral electrical activation of sympathetic discharge, were unaltered by nisoldipine administration. These data indicate that nisoldipine exerts differential effects on neurogenic and humoral adrenergic vasoconstriction.

Vanhouette and co-workers reported that the CEB lidoflazine antagonized the vasoconstrictor responses elicited by sympathetic nerve stimulation in isolated canine arteries and veins. While lidoflazine is a somewhat weak CEB, it appears to exert other actions on the cardiovascular system. On the other hand, nisoldipine is a potent and specific CEB that belongs to a chemically distinct class of agents. Thus specific drug actions and the fact that our experiments were performed in intact animals (whereas Vanhouette and colleagues used in vitro technique) probably help explain the differences between the two studies.

The mechanisms underlying nisoldipine's lack of effectiveness in attenuating neural vasoconstriction and potent actions on circulating norepinephrine are not readily apparent. It has been proposed that vascular responses, elicited by neurally released as opposed to circulating catecholamines, may be mediated by different adrenergic receptor subtypes \((\alpha_1 \text{ vs } \alpha_2)\) whose densities may themselves differ anatomically within the vasculature. Extrajunctional \( \alpha_1 \)-adrenergic receptors have been suggested to be preferentially activated by circulating catecholamines, with junctional postsynaptic \( \alpha_1 \)-adrenergic receptors and presynaptic \( \alpha_2 \)-adrenergic receptors being influenced primarily by neurally released norepinephrine. Indeed, nisoldipine has been reported to selectively inhibit \( \alpha_2 \)-rather than \( \alpha_1 \)-mediated vasoconstrictor responses in several animal models. Similarly, nifedipine, a dihydropyridine closely related to nisoldipine, has been demonstrated to selectively inhibit postsynaptic rather than presynaptic \( \alpha_2 \)-adrenergic receptor responses. If separate \( \alpha \)-adrenergic receptor populations are being activated by humoral and neural stimuli, then the selective depressant effect of nisoldipine on circulating norepinephrine possibly may result from the greater attenuation by nisoldipine of \( \alpha \)-adrenergic receptor mediated calcium entry in vascular smooth muscle cells that are preferentially acted on by circulating catecholamines. It is also possible that nisoldipine might increase the effective concentration of neurally released norepinephrine at the vascular neuroeffector junction by affecting release or reuptake mechanisms or both. Such a condition, if present coincident with reduced smooth muscle contractility caused by nisoldipine, also could account for the depressed responsiveness to circulating norepinephrine but not to nerve stimulation that we observed during nisoldipine administration. Additional studies are needed to distinguish between these possibilities.

Nisoldipine failed to affect baseline renal vascular resistance appreciably in both the conscious and anesthetized Sprague-Dawley rat. In previous studies we observed a similar lack of effect of nisoldipine on renal resistance, whereas nitrendipine and verapamil reduced renal resistance. In these earlier studies renal resistance appeared to be maintained by a reflex increase in neural vasoconstrictor tone, as abolition of reflex vasoconstriction by sinoaortic baroreceptor deafferentation unmasked a renal vasodilator action of nisoldipine. The present study complements these previous experiments by demonstrating the integrity of neurally mediated vasoconstrictor responses after nisoldipine administration.

**Conclusion**

This study indicates that the CEB nisoldipine antagonizes the vasoconstrictor actions of ANG II, norepinephrine, and epinephrine in conscious and anesthetized rats. In contrast, nisoldipine failed to antagonize neurally mediated vasoconstrictor responses. Thus nisoldipine appears to exert differential antagonistic actions on humoral rather than neurogenic pressor and vasoconstrictor responses in the intact rat.

**Acknowledgment**

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